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INDOLOPYRIDINES WITH A HETERO ATOM AT A POSITION OF FUSION.

8.* REDUCTIVE C-ALKYLATION OF INDOLO[2,1-A]ISOQUINOLINE

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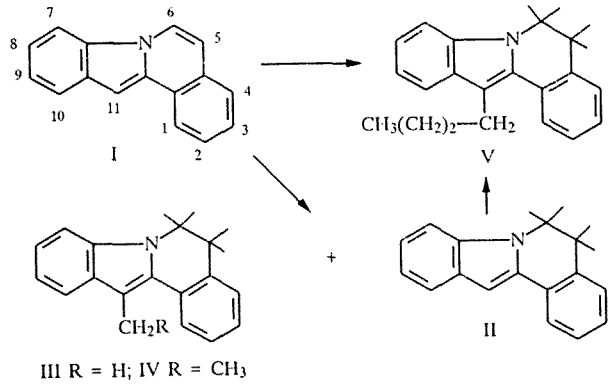
Indolo[2,1-a]isoquinoline was alkylated at $C_{(11)}$ under catalytic hydrogenation conditions over rhenium heptasulfide in a medium of various alcohols. It was shown that the alkylation occurs by an electrophilic substitution mechanism and the yield of the products increases with decreasing acidity of the alcohols.

Previously [2] we studied the catalytic hydrogenation of unsubstituted indolo[1,2-a]pyridine and its derivatives benzo-annelated (i.e., benzo-fused) at the pyridine ring. Here it was determined that over rhenium heptasulfide at 250°C and hydrogen pressure 140 atm the pyridine ring is hydrogenated initially and then the pyrrole ring, with the degree of hydrogenation of the heterocyclic fragments depending (with other conditions being similar) on the structure of the starting polycyclic compound.

Thus, in the case of indolo[2,1-a]isoquinoline (I) the pyrrole ring was not reduced at all and hydrogenation in benzene gave 5,6-dihydroindoloisoquinoline (II) in nearly quantitative yield.

Therefore, it is of interest to study the hydrogenation of compounds I and II in other media, e.g., in protic solvents, i.e., alcohols. In previous communications [1, 3], Ntaganda et al., showed the facileness of occurrence of various electrophilic substitution reactions in indolo[2,1-a]isoquinolines I and II at the free $C_{(11)}$ position of the pyrrole fragment; therefore, hydrogenation of aromatic indolopyridine I over Re_2S_7 in an alcohol medium could also give an alkyl derivative at the $C_{(11)}$ position. The possibility of N-alkylation of substituted pyridines during their hydrogenation over Re_2S_7 in alcohol [4, 5] indicates that the catalyst exhibits properties of a Lewis acid. In the case of indolo[2,1-a]isoquinolines I and II, such N-alkylation is precluded because of the fusion-site position of the nitrogen atom.



I V II III R = H; IV R = CH_3

*Communication 7, see [1]

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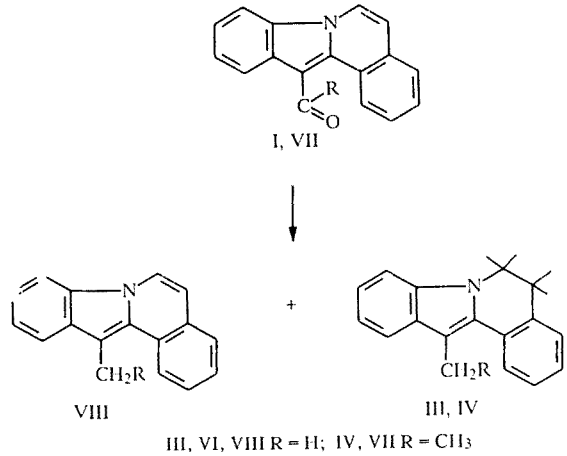
Hydrogenation of indolopyridine I in the presence of alcohols was carried out under conditions described in [2]. The alkylating agents were aliphatic alcohols, namely, methanol, ethanol, n-butanol, and isopropanol.* Here it was determined that in the first two cases there was formed in high total yield a mixture of 5,6-dihydroindoloisoquinoline II (64 and 41.5%, respectively) and 11-alkyl-5,6-dihydroindolo[2,1-a]isoquinolines (III, IV) (16 and 41.5%, respectively), and hydrogenation in n-butanol gave only 11-butyl derivative (V) in high yield (81%). In a medium of a secondary alcohol (2-propanol), alkylation did not occur, but only dihydroindolopyridine II was formed. To study the sequence of reactions, we also carried out an experiment on reductive alkylation of dihydro derivative II by n-butanol. It was determined that in this case the starting compound II was converted in high yield to 11-(n-butyl)-5,6-dihydroindoloisoquinoline (V). Thus, the results of the experiments with isopropanol and n-butanol indicate that initially isoquinoline I is hydrogenated to dihydroindoloisoquinoline II, which is then alkylated to 11-alkyl derivatives III-V.

It should be noted that the introduction of alkyl substituents in the $C_{(11)}$ position does not result (as in the case of unsubstituted dihydro derivative II) in hydrogenation of the pyrrole ring.

The increase of the relative yield of the products of C-alkylation in the series III → IV → V correlates with the decrease of the acidity of the primary aliphatic alcohols that were used, which confirms indirectly the presence and activity of the acid centers on the catalyst surface.

Despite their insignificant acidity, secondary and tertiary alcohols probably cannot be recommended for alkylation of indoloisoquinolines I and II under the given conditions because of stearic hindrances, i.e., access of secondary and tertiary carbocations to the unsubstituted position of the π-excess pyrrole fragment. Carrying out the reaction with m-cresol and mono- and triethanolamines (in benzene) did not give alkylation products: in all cases, only dihydroindoloisoquinoline II was recovered from the reaction mixture. When a large excess of triethanolamine was used, we observed complete deactivation of the catalyst (probably due to irreversible interaction of its acid centers with the nitrogen of triethanolamine). In this case, we recovered only the unreacted completely aromatic starting compound I. Because of the identical chromatographic mobility of the pairs of compounds II and III and of compounds II and IV, it was not possible to recover the 11-methyl (III) and 11-ethyl (IV) derivatives from the corresponding mixtures with dihydroindoloisoquinoline II. These compounds III and IV were obtained by back-synthesis, i.e., hydrogenation of 11-formyl- and 11-acetylindoloisoquinolines VI and VII in benzene under the above-described conditions.



III, VI, VIII R = H; IV, VII R = CH_3

The molecules of starting compounds VI and VII [3] contain two hetero atoms with an unshared electron pair, which can compete during chemisorption on acid centers of the catalyst. The experimental results show that these compounds preferentially react with the catalyst by their carbonyl oxygen because, after hydrogenation of formyl derivative VI for 2.5 h, mainly the formyl group was reduced with preservation of the aromatic structure of the pyridine fragment. In this case, mainly 11-methylindolo[2,1-a]isoquinoline (VIII) was formed (according to PMR data, the VIII:III ratio was ~4:1). As the reaction time was increased to 4 h, we observed subsequent hydrogenation of the pyridine ring (without involvement of the pyrrole part) to 11-methyl-5,6-dihydro derivative III in high yield. Similar, hydrogenation of 11-acetyl derivative VII to 11-ethyl-5,6-dihydroindoloisoquinoline (IV) occurred in 4 h.

*The pKa values were 15.1, 15.9, 16.1, and 17.1, respectively [6].

TABLE 1. Reagents and Reaction Products of Alkylation by Other Alcohols

Starting compound I, g (mmoles)	Alkylating agent-solvent (amount)	Reaction product	Mp, °C	M^+	Yield, %
0,5 (2,3)	Isopropanol (15 ml)	II	151...153	219	69
0,3 (1,4)	m-Cresol (15 g)	II	152...153	219	47
0,5 (2,3)	Monoethanolamine (0.31 g, 5.0 mmoles), benzene (15 ml)	II	153...154	219	64
0,5 (2,3)	Triethanolamine (0.4 g, 2.5 mmoles)	II	151...153	219	59
0,4 (1,8)	Triethanolamine (3.9 g, 26.4 mmoles)	I	200...205	217	60

*According to data of thin-layer chromatography and PMR, the starting compound was absent in all cases. The low yields of recovered compounds I and II are due to the formation of unidentified condensation products of complex structure.

EXPERIMENTAL

The recovery and purification of the obtained compounds were monitored by thin-layer chromatography on Silufol UV-254 plates with a 1:1 ether–heptane eluent and development by iodine vapor. Mass spectra were obtained with an MX-1303 spectrometer with ionizing-electron energy 70 eV. The PMR spectra were recorded with a Bruker WP-80 instrument (80 MHz) in $CDCl_3$ with TMS as the internal standard. The reagent ratios and the yields and melting points of the obtained compounds (III-V and VIII) are given in Table 1.

The data of elemental analysis corresponded to the calculated data.

Reductive C-Alkylation. An ampul containing a solution of 0.3-0.5 g (1.4-2.3 mmoles) of indoloisoquinoline I or 0.5 g (2.28 mmoles) of 5,6-dihydroindoloisoquinoline II in 15 ml of alcohol and 0.03-0.05 g of rhenium heptasulfide was placed in a rotating 150-ml autoclave, purged with nitrogen, filled with hydrogen to a pressure of 140 atm, heated to 250°C in 40 min, and kept at that temperature for 2.5-4 h. After cooling, the catalyst was separated, the solvent was driven off under vacuum, and the residue was purified and chromatographed on a column with silica gel. Compounds III and V were obtained from a mixture of compounds II and III and of II and V.

Hydrogenation of formyl VI and acetyl VII derivatives (0.1 g, (0.39 mmole) and 0.2 g (.76 mmoles), respectively) to alkyl derivatives III, IV, and VIII was carried out similarly in benzene (15 ml).

11-Methyl-5,6-dihydroindolo[2,1-a]isoquinoline (III). A. This compound was obtained as a mixture (total yield 80%) with 5,6-dihydro derivative II by alkylation of compound I by methanol. The III:II ratio, ~1:4, was determined according to PMR spectral data measuring the integrated intensity of the distinguished singlet peaks of protons of the $C_{(11)}$-methyl group of III (at 2.63 ppm) and the proton 11-H of dihydro derivative II (at 6.86 ppm).

B. This compound was obtained in pure form by 4-H hydrogenation of formyl derivative VI as crystals with mp 105-106°C, yield 72%, and M^+ 233. PMR spectrum: 2.63 (3H, singlet, CH_3); 3.13 (2H, triplet, J = 6 Hz, 5-H); 4.23 ppm (2H, triplet, J = 6 Hz, 6-H).

11-Ethyl-5,6-dihydroindolo[2,1-a]isoquinoline (IV). A. This compound was obtained in a mixture with dihydroindoloisoquinoline II (total yield 83%) by reductive alkylation of the starting compound I. According to the PMR spectral data, the IV:II ratio was 1:1 (determined by measuring the integrated intensity of the triplet peak at 1.37 ppm of the methyl group of compound IV and the singlet peak at 6.86 ppm of compound II).

B. This compound was obtained in 75% yield in pure form by hydrogenation of acetyl derivative VII as yellow crystals with mp 116-118°C and M^+ 247. PMR spectrum: 1.37 (3H, CH_2CH_3); 3.08 (2H, CH_2CH_3); 3.13 (2H, 5-H); 4.18 (2H, 6-H); 7.0-7.45 (6H, H_{arom}); 7.68-7.75 ppm (3H, 2H, 1- and 7-H).

11-(n-Butyl)-5,6-dihydroindolo[2,1-a]isoquinoline (V). A. This compound was obtained by alkylation of compound I and was recovered by crystallization from hexane in 81% yield as yellowish crystals with mp 86-89°C and M^+ 275. PMR spectrum: 1.0 (3H, CH_3); 1.2-1.85 (4H, $-CH_2CH_2-$); 3.03 (2H, $C_{(11)}-CH_2$-); 3.08 (2H, 5-H); 4.2 (2H, J = 5.3 Hz, 6-H); 7.0-7.45 (6H, 7.65 and 7.80 ppm (2H, 1- and 7-H).

B. This compound was obtained by alkylation of dihydro derivative II in 79% yield. According to its mp and PMR spectrum, it was identical to the sample obtained above. Temperature depression was not observed in a mixed sample.

11-Methylindolo[2,1-a]isoquinoline (VIII). This compound was obtained by 2.5-h hydrogenation of formyl derivative VI and was recovered by crystallization from hexane in 66% yield as yellow-green crystals with mp 128-130°C. PMR spectrum: 2.83 (3H, CH_3); 6.6 (1H, J = 7.2 Hz, 5-H); 7.15-7.95 (7H, H_{arm}); 8.03 (1H, J = 7.2 Hz, 6-H); 8.38 ppm (1H, J = 7.8 and 1.8 Hz, 1-H).

The reaction mixture contained 11-methyl-5,6-dihydroindoloisoquinoline III in III:VIII ratio ~1:4, which was determined by measuring the integrated intensity of singlet peaks of methyl groups at 2.63 (compound III) and 2.83 (compound VIII). Mass spectrum of VIII, *m/z* (%): M^+ 231 (100), 229 (39), 217 (29), 174 (41), 160 (36), 154 (57), 132 (37), 115.5 (26), 114.5 (23), 108.5 (10).

Reductive alkylation of 0.5 g (2.3 mmoles) of the starting I by isopropyl alcohol, m-cresol, and ethanolamine was similarly carried out. In all cases, alkylation did not occur. The results are given in Table 1.

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