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INDOLOPYRIDINES WITH A HETERO ATOM AT A POSITION OF FUSION.

5.* CATALYTIC SYNTHESIS OF INDOLO[2,1-A]ISOQUINOLINE BY PYROLYSIS OF BENZYLISOQUINOLINES

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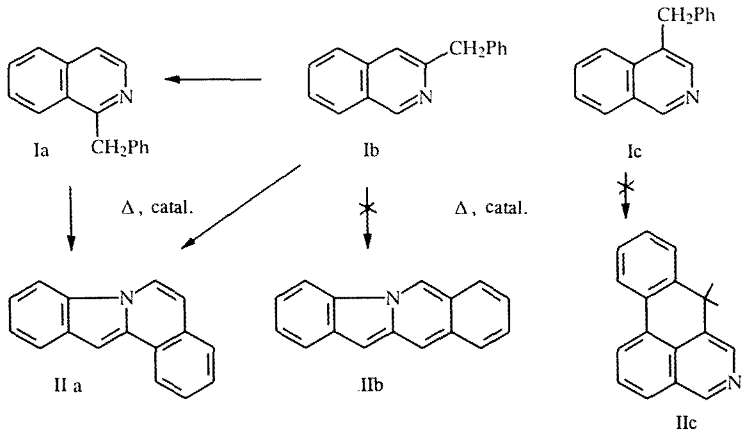
High-temperature heterocyclization of α-benzylisoquinolines on oxide-type catalysts gave angular indolo[2,1-a]isoquinoline.

Continuing our investigations [1-4] on the chemistry of indolopyridines with a nitrogen atom at the ring-fusion site (i.e., with an indolizine nitrogen atom), in the present paper we studied the possibility of conversion of isomeric benzylisoquinolines Ia-c to polycycles IIa-c on oxide-type catalysts. It was determined that 1-benzylisoquinoline Ia is converted in moderate yields to indolo[1,2-a]isoquinoline (IIa) during pyrolysis over copper at 590°C [5] or in the absence of catalysts at 650-700°C [3]. To increase the yield of compound IIa in order to carry out the conversion Ia → IIa, we used catalysts based on aluminum oxide (catalyst 380 [6],[†] (see the experimental part) and chromium oxide (Catalyst K-16 [7]). The first catalyst was found to be virtually inactive at temperatures below 500°C. In dehydrocyclization, its high activity was observed in the range of 540-600°C. At 540°C, the degree of conversion of 1-benzylisoquinoline reached 60%, and the yield of polycycle IIa was 51% on the basis of compound Ia. Increasing the temperature to 600°C resulted in almost complete conversion of compound Ia (~93%), but the selectivity of the reaction in this case decreased by 20%, and the yield of indoloisoquinoline IIa increased to only 58%.



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[*] For Communication 4 see [1].

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TABLE 1. Composition of Products of Ladenburg–Chichibabin Reaction

Compound	M^+	R_f	Mp, °C	Content, %[*2]			
				expt. 1	expt. 2	expt. 3	expt. 4
Diphenylethane	182	0,9	50...52	15,5	18,0	—	—
Ia	219	0,6	52...54 (56)	70,0	70,0	88,0	82,0
Ib	219	0,45	100...103 (104)	4,5	4,0	4,2	6,0
Ic	219	0,42	115...117 (118)	10,0	9,0	7,8	12,0

[*] The melting point according to [2] is given in parentheses.

[*2] The composition of the reaction mixture was determined according to GLC data (in expts. 1 and 2, before separation of neutral compounds; in expt. 3, after separation of neutral compounds) and according to data of PMR spectra (in expt. 4, after removal of neutral conversion products). Integration in the PMR spectrum was carried out with respect to singlet peaks of methylene protons at 4.65 (Ia), 4.48 (Ib), and 4.30 ppm (Ic).

When Catalyst K-16 was used, dehydroheterocyclization product IIa was formed at 600°C in higher yield (~70%) with complete conversion of the starting Ia. Thus, the oxide catalysts that were used were found to be sufficiently effective at moderate temperatures in the conversion Ia → IIa.

In studying the possibility of conversion of 3-benzylisoquinoline (Ib) to linear indolo[1,2-b]isoquinoline (IIb) under analogous conditions, it was determined that even at 400°C (Catalyst K-16) compound Ib underwent conversion (70%) with formation of isoquinoline, diphenylethane, 1-benzylisoquinoline (Ia), and angular polycycle IIa (12%). Complete conversion of 3-benzylisoquinoline was attained at 500°C, and the yield of polycycle IIa increased to 60%. From isomeric compound Ia, at this temperature, only an insignificant amount (3%) of polycycle IIa was formed. The fact that the indoloisoquinoline that was recovered as a result of pyrolysis of 3-benzylisoquinoline had an angular structure (and not the expected linear one) was determined according to the identity of its PMR spectrum, the melting point, and the absence of temperature depression with a known sample of IIa. The pyrolysis data indicate significantly lower thermodynamic stability of compound Ib and linear indoloisoquinoline IIb (having on o-quinoid structure) in comparison with 1-benzylisoquinoline Ia (24%) and angular indoloisoquinoline IIb, respectively, which are isomeric to it. In this regard, we can mention the data of [8] about facile debenzylation of α-benzyl(o-chlorobenzyl)isoquinolines (by 80%) in an attempt to synthesize their quaternary salts with ethyl bromoacetate even without heating.

Unlike in the case of α-benzyl-substituted isoquinolines Ia and Ib, 4-benzylisoquinoline (Ic), isomeric to them and having a benzyl group in the β position, was rather stable under the studied pyrolysis conditions and did not undergo significant debenzylation or conversion to polycycle IIc at ≤500°C.

EXPERIMENTAL

Thin-layer chromatography was carried out on Silufol UV-254 plates, and the eluent was ether–hexane (1:1). The substances were purified and recovered on chromatographic columns with silica gel L 40/100. For GLC analysis, we used an LKhM-7A instrument with a 1.8-m × 3-mm column filled with Chromosorb W with 5% silicone rubber SKTF at 150-220°C, a thermal-conductivity detector, and helium carrier gas with a flow rate of 75 ml/min. The PMR spectra were recorded on a Bruker WP-80 spectrometer, and the mass spectra were recorded on an MKh-1303 instrument.

1-(3-, 4-)-Benzylisoquinolines Ia-c. A mixture of 38.5 g (0.3 mole) of isoquinoline and 51.9 g (0.41 mole) of benzyl chloride was boiled for 3 h, 0.38 g of copper filings was added, and the whole was heated for 8 h at 230-250°C. Completion of the reaction was monitored by thin-layer chromatography and GLC. The hot solution was poured onto ice (200 g), 0.3 liter of water was added, the whole was acidified with 10% hydrochloric acid to pH 1, and neutral substances were extracted with ether. The aqueous layer was alkalized with a 20% KOH solution, benzylisoquinolines were extracted with ether, and the extract was dried with magnesium sulfate. After the solvent was driven off, 37.2 g (57%) of a mixture of benzylisoquinolines was obtained as a thick dark-brown oil. A mixture of 2.4 g of benzylisoquinolines Ia-c was deposited onto a column with silica gel (150 g) and eluted with hexane (0.5 liter) and then with a 1:1 ether–hexane mixture. First, 1.56 g of isomer Ia was obtained, then 0.024 g of compound Ib, 0.22 g of a mixture of benzylisoquinolines Ib and Ic, and finally 0.04 g of 4-benzylisoquinoline (Ic). Crystallization of a mixture of compounds Ib and Ic from hexane gave an additional 0.05 g of pure compound Ic. The crystallization mother liquor contained a mixture of 3- and 4-isomers (in a 1:2 ratio), which was then used without separation for synthesis of indolopyridine IIa.

Pyrolysis of 1-Benzylisoquinoline Ia on Catalyst 380. A. Through a catalytic quartz tube containing 4.2 g of Catalyst 380 (89% Al_2O_3, 5% Cr_2O_3, 5% La_2O_3, and 1% K_2O [6]) was passed 10 ml of benzene at 500°C for 30 min and then 2.5 g (11.4 mmoles) of compound Ia in 15 ml of benzene for 1 h. The obtained condensate was filtered through a short column with 10 g of silica gel, and the adsorbent layer was washed with ether, the eluates were combined, and, after the solvent was driven off, 2.4 g of a residue was obtained which, according to GLC data, contained 0.08 g (3%) of indoloisoquinoline IIa, 2.27 g of unreacted compound Ia,a and 0.05 g of biphenyl.

B. Similarly, 1.5 g (50.8%) of polycycle IIa and 1.2 g (37%) of unreacted compound Ia (GLC) were obtained at 540°C from a solution of 3.0 g (13.7 mmoles) of benzylisoquinoline Ia in 15 ml of toluene.

C. Similarly, a catalyzate which, according to GLC data, contained 10.1 g (58.3%) of polycycle IIa and 1.3 g of unreacted compound Ia was obtained at 600°C from a solution of 17.5 g (79.9 mmoles) of the starting 1-benzylisoquinoline Ia in 100 ml of toluene. The mixture was separated on a column with silica gel. First, 9.7 g (56%) of indoloisoquinoline IIa with R_f 0.8 and mp 214-216°C was recovered [5]; the PMR spectrum (DMSO-d_6) was identical to the spectrum described in [3]. Subsequently, 1.1 g of the starting 1-benzylisoquinoline (Ia) was eluted.

D. Similarly, pyrolysis was carried out using commercial Catalyst K-16 (51.3% Cr_2O_3, 25.2% Fe_2O_3, 23% ZnO, and 0.5% SiO_2 [7]). After passage of a solution of 7.8 g (35.6 mmoles) of compound Ia in 50 ml of benzene over this catalyst (4 g), 5.4 g (70%) of polycycle IIa was recovered by crystallization from benzene.

Pyrolysis of 4-Benzylisoquinoline Ic and Mixture of 3- and 4-Benzylisoquinolines Ib and Ic. A. Similarly to what was described above, pyrolysis of 4-benzylisoquinoline was carried out by passing a solution of 1 g of 4-benzylisoquinoline Ic in 10 ml of benzene through a reactor with 4 g of Catalyst K-16 for 30 min at 500°C. After purification on a short column with 15 g silica gel, we obtained 0.9 g of a crystalline residue, which, according to thin-layer chromatography, GLC, and PMR data, consisted of 93% unreacted compound Ic.

B. Similarly, passing a solution of a mixture of 0.67 g (3 mmoles) of 3-benzylisoquinoline (Ib) and 1.3 g (6 mmoles) of 4-bnezylisoquinoline Ic in 20 ml of benzene for 1 h at 400°C, after chromatographic purification we obtained 1.8 g of a catalyzate which, according to thin-layer chromatography, GLC, and PMR spectra, contained six substances: 0.05 g (6% based on the total of Ib and Ic) of diphenylethane; 0.1 g (9% based on the total of Ib + Ic) of isoquinoline, R_f 0.4; 0.08 g (12% based on Ib) of indoloisoquinoline IIa, R_f 0.8; 0.16 g (24% based on Ib) of 1-benzylisoquinoline; 0.2 g (30%) of unreacted compound Ib; and 1.2 g (92%) of unreacted compound Ic.

C. Similarly, at 500°C from 2.0 g of a mixture of benzylisoquinolines Ib and Ic (in a 1;2 ratio), we obtained 1.77 g of catalyzate, which was separated on a colum with 100 g of silica gel by eluting successively 0.1 g (12%) of diphenylethane, 0.4 g (60%) of angular indoloisoquinoline IIa (the PMR spectrum and the melting point were identical to those of a known sample, and there was no temperature depression in a mixed sample), 0.08 g (12%) of compound Ia, which was formed as a result of transbenzylation of 3-benzylisoquinoline Ib, and 1.08 g (83%) of unreacted compound Ic. The degree of conversion of 3-benzylisoquinoline was 100% in this experiment.

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