Chemistry of Heterocyclic Compounds, Vol. 31, No. 3, 1995

SYNTHESIS AND ISOMERIZATION RECYCLIZATION OF PYRAZINO[1,2-*a*]INDOLES

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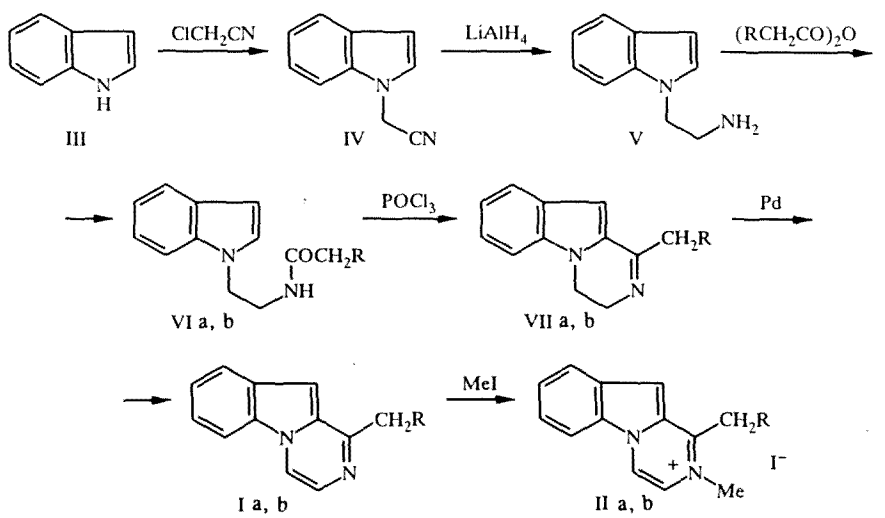
A method for synthesis of pyrazino[1,2-a]indoles with alkyl substituents in position 1 was developed based on indole and isomerization recyclization of their quaternary salts into 9-aminopyrido[1,2-a]indole derivatives was conducted.

As demonstrated previously [1, 2], 1-alkyl-substituted pyrrolo[1,2-*a*]pyrazinium salts are rearranged into 8-aminoindolizine derivatives under the effect of bases. This reaction is a new method for synthesis of the indolizine nucleus and also the first example of enamine rearrangement in the pyrazine series [3].

Recyclization of benzo-annelated analogs of pyrrolo[1,2-*a*]pyrazines — pyrazino[1,2-*a*]indoles I, in conditions of enamine rearrangement can yield the corresponding 9-aminopyrido[1,2-*a*]indole derivatives, which are potential biologically active compounds and difficult to obtain by other methods [4]. The reaction of their methyl iodides II with an alcohol solution of methylamine was investigated to determine the possibility of such rearrangement of pyrazino[1,2-*a*]indoles I. The quaternary salts of pyrazino[1,2-*a*]indoles IIa, b were synthesized according to Scheme 1.

Scheme 1



I, II, VI, VII a R = H, b R = Me

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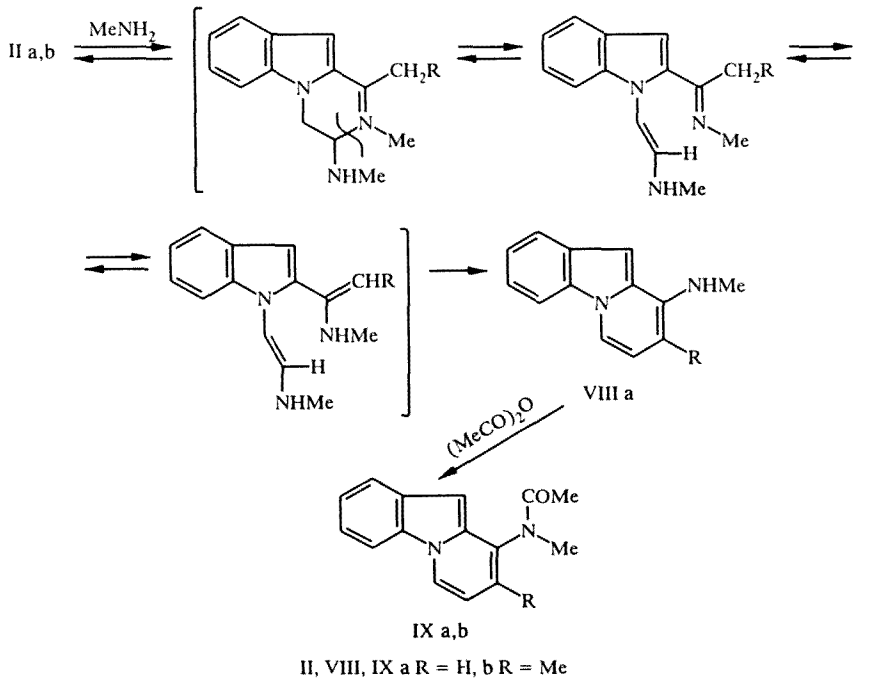
 0009-3122/95/3103-0284$12.50

The stage of alkylation of indole with chloroacetonitrile should be considered in more detail. 1-(Cyanoethyl)indoles containing acceptor substituents in the pyrrole part of the indole nucleus were previously obtained by direct N-alkylation, and this significantly facilitated incorporation of a cyanomethyl group in position 1 of the indole [5]. Alkylation of unsubstituted indole with chloroacetonitrile creates difficulties, on one hand due to the low N—H acidity of the unsubstituted indole molecule and the ambidentate character of the anion formed (alkylation can take place ambiguously and also involve position 3). On the other hand, chloroacetonitrile is not very stable in the presence of bases and its reactivity is low. It was thus necessary to reject the traditional methods of alkylation of indoles using alkali metal hydrides, alkoxides, or amides, as well as use of the method of interphase catalysis (MIC) in a liquid/liquid system. A method of alkylation of unsubstituted indole with chloroacetonitrile was developed using MIC in a liquid/solid phase system. Benzene was selected as the solvent, and a mixture of solid sodium hydroxide and calcium carbonate in the molar ratio of 2:1 was selected as the base. To prevent decomposition, the chloroacetonitrile was gradually added to a boiling benzene solution containing the indolyl cation and catalyst — tetrabutylammonium bromide.

1-(2-Aminoethyl)indole (V), prepared by reduction of 1-(cyanoethyl)indole (IV) with lithium aluminohydride in absolute ether, was acylated with acetic or propionic anhydride without separation, with formation of amides VIa, b. Cyclization of the amides was conducted with phosphorus oxychloride in *o*-xylene. Dehydrogenation of the 3,4-dihydroyrazino[1,2-*a*]indoles VII obtained into their aromatic derivatives I was complicated by the fact that compounds VII and I were not very stable when heated (especially in solutions). The most satisfactory result was obtained by dehydrogenation of 3,4-dihydropyrazino[1,2-*a*]indoles by heating with palladium black with no solvent.

Scheme 2



II, VIII, IX a R = H, b R = Me

The reaction of 1-methylpyrazino[1,2-*a*]indole methyl iodide (IIa) with 40% alcohol solution of methylamine with heating in a sealed ampul at 100-110°C leads to formation of 9-methylaminopyrido[1,2-*a*]indole (VIIIa) with a yield of 29%. 9-Aminopyrido[1,2-*a*]indole derivatives VIII are not very stable in air and in solutions, and acylation at the amino group with formation of 9-N-methyl-N-acetylpyrido[1,2-*a*]indoles IX increases their stability. In recyclization of 1-ethylpyrazino[1,2-*a*]indole (IIb) salts, it was only possible to separate the acetyl derivative of 9-aminopyrido[1,2-*a*]indole IXb with an alkyl substituent in position 8. Incorporation of alkyl substituents in the pyridine ring of the aminopyrido[1,2-*a*]indole molecule probably decreases the stability of these compounds. A similar phenomenon was also observed for 8-aminoindolizines in [1].

TABLE 1. Constants, Yields, and Mass Spectra of the Synthesized Compounds

Compound	Empirical formula	Mp, °C	Mass spectrum, m/z (I_{rel}, %)	Yield, %
Ia	$C_{12}H_{10}N_2$	255...256*	—	33
Ib	$C_{13}H_{12}N_2$	47...48	—	28
IIa	$C_{13}H_{13}N_2I$	260...262	—	97
IIb	$C_{14}H_{15}N_2I$	258...260	—	78
IV	$C_{10}H_8N_2$	74...75	—	53
V	$C_{10}H_{12}N_2$	206...207*	—	95
VIa	$C_{12}H_{14}N_2O$	Oil	—	95
VIb	$C_{13}H_{16}N_2$	Oil	216(M^+, 37), 144(13), 143(94), 131(12), 130(100), 117(8), 103(14), 77(17), 57(13)	91
VIIa	$C_{12}H_{12}N_2$	80...81	—	72
VIIb	$C_{13}H_{14}N_2$	70...71	198(M^+,100), 197(77), 196(3), 182(3), 170(14), 154(10), 142(11), 128(6), 122(6), 115(12)	49
VIIIa	$C_{13}H_{12}N_2$	Oil	196(M^+,100), 181(13), 168(68), 154(50), 140(16), 127(12), 115(6), 98(11), 89(10), 77(11)	29
IXa	$C_{15}H_{14}N_2O$	Oil	238(M^+, 54), 209(9), 195(82), 183(22), 167(93), 154(26), 140(27), 127(11), 73(22), 56(100)	59
IVb	$C_{16}H_{16}N_2O$	Oil	252(M^+, 58), 238(9), 223(3), 209(64), 197(33), 195(18), 181(22), 180(31), 167(25), 56(100)	50

*Picrate.

We can hypothesize that 9-aminopyrido[1,2-*a*]indoles are formed according to Scheme 2, similar to formation of 8-aminoindolizines from 1-alkyl-substituted pyrrolo[1,2-*a*]pyrazines in [1]. The nucleophile attacks the pyrazino[1,2-*a*]indole molecule at the $C_{(3)}$ atom, which causes opening of the pyrazine ring at the $C_{(3)}$—$N_{(2)}$ bond. Subsequent cyclization of the intermediate takes place at the β-carbon atom of the enamine fragment and results in formation of a pyridine nucleus.

The possibility of recyclization of the pyrazino[1,2-*a*]indole system into pyrido[1,2-*a*]indole was thus demonstrated in quaternary salts of pyrazino[1,2-*a*]indoles with an alkyl substituent in position 1, and previously unknown 9-aminopyrido[1,2-*a*]indoles were synthesized. The lower yields of the products of recyclization in comparison to rearrangement of pyrrolo[1,2-*a*]pyrazinium salts into 8-aminoindolizines are probably due to the lower stability of both pyrazino[1,2-*a*]indoles and 9-aminopyrido[1,2-*a*]indoles in the conditions of the recyclization reaction.

EXPERIMENTAL

The ^1H NMR spectra of compounds V and VIa were made on a Tesla BS-467 (60 MHz), and the ^1H NMR spectra of compounds Ia, b, IV, VIb, VIIa, b, VIIIa, IXa, b and the ^{13}CNMR spectrum of compound IV were made on a Varian VXR-400 in $CDCl_3$, with TMS as internal standard. The mass spectra were made on a MX-1321A with 70 eV ionization energy. The evolution of the reactions was monitored by TLC on Silufol-UV 254 plates. The yields, constants, and mass spectra of the compounds obtained are reported in Table 1, and the other spectral characteristics are presented in Table 2.

Elemental analysis of compounds Ia, IV, V, and VIIa for C, H, and N corresponded to the calculated values.

1-(Cyanomethyl)indole (IV). A mixture of 0.05 mole of indole, 0.2 mole of finely ground solid sodium hydroxide, 0.1 mole of calcium carbonate, 4.6 mmole of tetrabutylammonium bromide, and 1 ml of water in 100 ml of benzene was boiled for 30 min until it turned dark green. A solution of 0.16 mole of chloroacetonitrile in 30 ml of benzene was then slowly added by drops and the reaction mixture was boiled for 2 h. The mixture was poured into 200 ml of cold water and the organic layer was separated. The aqueous layer was extracted with benzene, and the benzene extracts were combined and dried with calcium chloride. The solvent was evaporated. The residue was separated on a column with 5/40 μ silica gel in benzene—hexane system, 1:1.

TABLE 2. ^1H and ^{13}C NMR Spectra of the Synthesized Compounds

Compound	NMR spectrum, δ, ppm (J, Hz)	
I a	^1H:	2,75 (3H, s, 1-CH_3), 6,94 (1H, s, 10-H), 7,36...7,43 (2H, m, 7-, 8-H), 7,45 (1H, d, J_{34} = 4,9, 3-H), 7,84...7,89 (2H, m, 6-,9-H), 8,00 (1H, d, J_{43} = 4,9, 4-H)
I b	^1H:	1,4 (3H, t, J = 7,5, CH_3), 3,1 (2H, q, J = 7,5, CH_2CH_3), 6,9 (1H, s, 10-H), 7,38...7,44 (2H, m, 7-, 8-H), 7,5 (1H, d, J_{34} = 4,9, 3-H), 7,86...7,91 (2H, m, 6-, 9-H), 8,04 (1H, d, J_{43} = 4,9, 4-H)
IV	^1H:	4,5 (2H, s, CH_2CN), 6,67 (1H, d, J_{32} = 3,2, 3-H), 6,82 (1H, d, J_{23} = 3,2, 2-H), 7,11...7,24 (3H, m, 4-, 5-, 6-H), 7,59 (1H, d, J_{76} = 7,7, 7-H)
	^{13}C:	33,618 (CH_2), 103,623 ($C_{(3)}$), 108,672 ($C_{(7)}$), 114,469 (C≡N), 120,536 ($C_{(6)}$), 121,218 ($C_{(4)}$), 122,558($C_{(5)}$), 127,088 ($C_{(2)}$), 128,630 ($C_{(3a)}$), 135,380 ($C_{(7a)}$)
V	^1H:	0,8 (2H, br.s, NH_2), 2,8 (2H, t, J = 6, CH_2-indole), 3,8 (2H, t, J = 6, CH_2NH_2), 6,65 (1H, d, J_{32} = 3, 3-H), 7,2 (1H, d, J_{23} = 3, 2-H), 7,2...7,7 (3H, m, 4-, 5-, 6-H), 7,9 (1H, m, 7-H)
VI a	^1H:	1,65 (3H, s, CH_3), 3,4 (2H, t, J = 6, CH_2NH), 4,2 (2H, t, J = 6, CH_2-indole), 6,1 (1H, br.s, NH), 6,35 (1H, d, J_{32} = 3, 3-H), 6,9 (1H, d, J_{23} = 3, 2-H), 6,9...7,3 (3H, m, 4-, 5-, 6-H), 7,5 (1H, m, 7-H)
VI b	^1H:	1,07 (3H, t, J = 7,5, CH_3), 2,05 (2H, q, J = 7,5, CH_2CH_3), 3,51 (2H, t, J = 5,9, CH_2NH), 4,50 (2H, t, J = 5,9, CH_2-indole), 5,5 (1H, br.s, NH), 6,50 (1H, d.d, J_{32} = 3,2, J_{37} = 0,8, 3-H), 7,03 (1H, d, J_{23} = 3,2, 2-H), 7,10 (1H, d.d.d, J_{67} = 8, 6-H), 7,20 (1H, d.d.d, J_{54} = 8,2, 5-H), 7,33 (1H, d.m, J_{45} = 8,2, 4-H), 7,62 (1H, d.m, J_{76} = 8, J_{73} = 0,8, 7-H)
VII a	^1H:	2,43 (3H, s, CH_3), 4,01...4,05 (4H, m, 3-, 4-CH_2), 6,79 (1H, s, 10-H), 7,11...7,17 (1H, d.d.d, J_{89} = 8,0, J_{87} = 8,0, J_{86} = 1,5, 8-H), 7,28...7,35 (2H, m, 7-, 9-H), 7,68 (1H, d.m, J_{67} = 8,0, 6-H)
VII b	^1H:	1,3 (3H, t, J = 7,5, CH_3), 2,75 (2H, q, J = 7,5, CH_2CH_3), 4,01...4,07 (4H, m, 3-, 4-CH_2), 6,79 (1H, d, J_{106} = 0,8, 10-H), 7,14 (1H, d.m, J_{89} = 8,0, J_{87} = 8,0, J_{86} = 1,4, 8-H), 7,29 (1H, d.m, J_{76} = 8,0, J_{78} = 8,0, J_{79} = 1,1, 7-H), 7,38 (1H, d.m, J_{98} = 8,0, 9-H), 7,68 (1H, d.m, J_{67} = 8,0, J_{610} = 0,8, 6-H)
VIII a	^1H:	3,0 (3H, s, CH_3), 4,1 (1H, br.s, NH), 5,91 (1H, d, J_{87} = 7,0, 8-H), 6,48 (1H, d.d, J_{78} = 7,0, J_{76} = 7,0, 7-H), 6,50 (1H, s, 10-H), 7,25 (1H, d.d.d, J_{21} = 8,3, J_{23} = 8,3, 2-H), 7,32 (1H, d.d.d, J_{34} = 8,3, J_{32} = 8,3, 3-H), 7,77 (1H, d.m, J_{43} = 8,3, 4-H), 7,83 (1H, d.d, J_{12} = 8,3, 1-H), 7,86 (1H, d, J_{67} = 7,0, 6-H)
IX a	^1H:	1,97 (3H, s, $COCH_3$), 3,35 (3H, s, NCH_3), 6,52 (1H, d.d, J_{76} = 6,9, J_{78} = 6,9, 7-H), 6,62 (1H, s, 10-H), 6,82 (1H, d.d, J_{87} = 6,9, J_{86} = 0,8, 8-H), 7,35 (1H, d.d.d, J_{21} = 8,3, J_{23} = 8,2, J_{24} = 1,2, 2-H)
IX b	^1H:	7,41 (1H, d.d.d, J_{32} = 8,2, J_{34} = 8,0, J_{31} = 0,8, 3-H), 7,82 (1H, d.m, J_{43} = 8,0, 4-H), 7,91 (1H, d.d, J_{12} = 8,3, J_{13} = 0,8, 1-H), 8,33 (1H, d.m, J_{67} = 6,9, 6-H), 1,88 (3H, s, $COCH_3$), 2,23 (3H, s, 8-CH_3), 3,28 (3H, s, NCH_3), 6,38 (1H, d, J_{76} = 7,2, 7-H), 6,48 (1H, s, 10-H), 7,30 (1H, d.d.d, J_{21} = 8,3, J_{23} = 8,2, J_{24} = 1,1, 2-H), 7,38 (1H, d.d.d, J_{32} = 8,2, J_{34} = 8,0, J_{31} = 0,9, 3-H), 7,78 (1H, d.m, J_{43} = 8,0, 4-H), 7,85 (1H, d.d, J_{12} = 8,3, J_{13} = 0,9, 1-H), 8,23 (1H, d, J_{67} = 7,2, 6-H)

1-(2-Aminoethyl)indole (V). A solution of 0.027 mole of 1-(cyanomethyl)indole in 20 ml of ether was added by drops to a mixture of 0.04 mole of lithium aluminohydride in 50 ml of absolute ether, heated to boiling. The reaction mixture was boiled for 2-2.5 h until the green coloration disappeared. The excess lithium aluminohydride was decomposed with water until the solution turned pink. The sediment was filtered off, washed with ether, the ether extracts were combined, and the solvent was evaporated.

1-(2-Acylaminoethyl)indoles (VIa, b). A two-fold excess of acetic or propionic anhydride was added to a solution of 2-5 g of 1-(2-aminoethyl)indole in 5-10 ml of benzene. The reaction mixture was left for 24 h. The solvent and excess anhydride were evaporated and separated in a column with silica gel in the benzene—ethyl acetate system, 2:1.

3,4-Dihydropyrazino[1,2-*a*]indoles (VIIa, b). A five-fold excess of phosphorus oxychloride in 50 ml of *o*-xylene was heated to boiling and a solution of 1-2 g of the corresponding 1-(2-acylaminoethyl)indole in 20-30 ml of *o*-xylene was added by drops. The reaction mixture was boiled for 1.5-3 h, 10 ml of water was added, and it was boiled for 30 min until the sediment totally dissolved. A solution of base was added until the aqueous layer clarified. The organic layer was separated, dried with calcium chloride, the solvent was evaporated, the residue was extracted with hexane, and the hexane was evaporated.

Pyrazino[1,2-*a*]indoles (Ia, b). Here 1-2 g of 3,4-dihydropyrazino[1,2-*a*]indole was heated with palladium black at 210-230°C for 2-4 h until evolution of hydrogen stopped. The reaction mixture was dissolved in acetone, the palladium was filtered off, the solvent was evaporated, and the sediment was separated in a column with silica gel in hexane—ethyl acetate system, 1:1.

Pyrazino[1,2-*a*]indole Methyl Iodides (IIa, b). An excess (2-3 ml) of methyl iodide was added to 0.1-0.2 g of the corresponding pyrazino[1,2-*a*]indole. The mixture was left for 24 h. The precipitated crystals were filtered off and washed with hexane.

Recyclization of Pyrazino[1,2-*a*]indole Methyl Iodides IIa, b. A mixture of 0.5-1 mmole of salt II and 5 ml of a 40% alcohol solution of methyl amine was heated in a sealed ampul at 100-110°C for 10-15 h. The alcohol was evaporated.

A. **9-N-Methylaminopyrido[1,2-*a*]indole (VIIIa)**. The sediment was separated in a column with silica gel in the hexane—ethyl acetate system, 3:1 .

B. **9-N-Acetyl-N-methylaminopyrido[1,2-*a*]indoles (IXa, b)**. The sediment was dissolved in 3 ml of benzene and an excess (1-3 ml) of acetic anhydride was added. The solvent and acetic anhydride were evaporated. The sediment was separated in a column with silica gel in the hexane—ethyl acetate system, 3:1.

The research was conducted with the financial support of the Russian Fund for Fundamental Research (Project Code 93-03-4593) and ISF (Project Code NBDOOO).

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