N-ANIONS OF HETEROAROMATIC AMINES

VI.* ALKYLATION OF N-ANIONS OF HETEROAROMATIC AMINES IN LIQUID AMMONIA WITH ALKYL HALIDES AND BENZYL CHLORIDE

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The alkylation of the N-anions of 2- and 4-aminopyridines, 1-aminoisoquinoline, and 2-amino-1-ethylbenzimidazole with C_2-C_4 alkyl halides in liquid ammonia leads to the formation of a mixture of the products of mono- and dialkylation at the NH_2 group (usually with a predominance of the latter). The role of stepwise processes and the yield of the dialkyl derivative increase on passing from alkyl bromides to iodides and from the heavier and branched radicals (C_4H_9, i-C_3H_7) to lighter radicals (C_2H_5).

As has recently been shown, in liquid ammonia the N-anions of heteroaromatic amines methylate almost exclusively to dimethylamino derivatives, regardless of the ratio of the N-anion to the methylating agent [2, 3]. Considering the preparative importance of this reaction, in the present work we have studied the alkylation of the N-anions of a number of heteroaromatic amines using C_2-C_4 alkyl halides and benzyl chloride.

The N-anions were obtained by the action of freshly prepared sodium amide on the amines. It was found that it is also possible to use technical sodium amide synthesized by the high-temperature method [4].

It was found that the stepwise nature of the alkylation reaction in liquid ammonia is also retained in these cases, but its relative proportion increases considerably on passing from methyl to heavier hydrocarbon radicals and becomes moderate even for butyl (Table 1). On passing from ethyl to propyl and then to butyl halides, the yield of tertiary amine decreases, while the yield of monoalkylated derivative increases. It follows from Table 1 that the stepwise nature of the process is expressed to a greater extent for the alkyl iodides than for the bromides.

Similarly, according to the results that French authors [5] have recently obtained for the N-anions of 4-aminoquinaldine and β-unsaturated alkyl halides, the bromides favor the formation of dialkylamine derivatives to a greater extent than the chloride.

The yield of alkylation products increases if two moles of sodium amide and alkyl halide are taken per mole of amine (Table 2). Under these conditions, the amount of dialkylamino derivative usually exceeds 50%, and in a number of cases (4-diethylaminopyridine) it reaches 75%. In addition to the tertiary amine, no little amount of secondary amine is formed (with the exception of the case of 4-aminopyridine); however, their separation by means of column chromatography on alumina presents no difficulties. A noteworthy feature of alkylation in liquid ammonia, in view of the extremely mild conditions, is the absence of resinification and of the formation of quaternary salts and other by-products. Consequently, if the total yield of mono- and dialkylamino derivative is less than 100%, the residue consists of unchanged initial amine.

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[*] For communication V, see [1].

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TABLE 1. Alkylation of the Monoanion of 2-Amino-1-ethylbenzimidazole in Liquid Ammonia with One Equivalent of a C_2-C_4 Alkyl Halide*

Alkyl halide	Yield, %	
	$N(Alk)_2$ †	NHAlk
C_2H_5Br	19	33
C_2H_5I	26	15
C_3H_7Br	11	53
C_3H_7I	22	40
C_4H_9Br	10	52
C_4H_9I	15	46

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* The amount of $NaNH_2$ taken to produce the monoanion was also equimolecular, i.e., 1 : 1.

†The yields given in the second column were calculated with respect to the amount of amine taken. It is obvious that at a ratio of amine to RX of 1 : 1 the theoretical yield of dialkylamino derivative cannot exceed 50%. Under these conditions, the amount of unchanged amine is equal to the yield of tertiary amine. Calculated on the alkyl halide taken, all the yields given in the second column must be doubled.

TABLE 2. Results of the Alkylation of N-Anions $RNH^- + AlkX \rightarrow RNHAlk + RN(Alk)_2$

R	AlkX	Ratio, moles			Yield, %	
		RNH_2	$NaNH_2$	AlkX	RNHAlk	$RN(Alk)_2$
α-Pyridyl	C_2H_5Br	1	2	2	38	41
The same	C_3H_7I	1	2	2	49	16
” ”	i-C_3H_7Br	1	2	2	13	—
” ”	i-C_3H_7I	1	2	2	32	—
” ”	C_4H_9Br	1	2	2	49	24
γ-Pyridyl	C_2H_5Br	1	1	1	—	38
The same	The same	1	2	2	—	73
Isoquinolin-1-yl	C_2H_5Br	1	2	2	27	30
The same	The same	1	2	3	31	40
” ”	” ”	1	3	3	35	46
” ”	C_2H_5I	1	2	2	27	47
” ”	C_3H_7Br	1	2	2	32	40
” ”	C_3H_7I	1	2	2	19	57
” ”	C_4H_9Br	1	2	2	63	8
” ”	The same	1	3	3	43	40
” ”	C_4H_9I	1	2	2	37	53
1-Ethylbenzimidazol-2-yl	C_2H_5Br	1	2	2	21	58
The same	C_3H_7Br	1	2	2	33	27
” ”	C_3H_7I	1	2	2	—	62
” ”	C_4H_9Br	1	2	2	34	22
” ”	The same	1	2	3	40	26
” ”	” ”	1	3	3	34	30
” ”	C_4H_9I	1	2	2	20	40
” ”	$C_6H_5CH_2Cl$	1	2	2	41	30

The alkylation of N-anions with isopropyl halides was performed for 2-aminopyridine. The only reaction product in this case was 2-isopropylaminopyridine. The low yield of secondary amine – 13-32% – and the difficulty of formation of the tertiary amine are obviously due to steric effects, and also to the tendency of isopropyl halides to undergo elimination reactions of the E_2 type under the action of bases.

In the benzylation of the N-anions of 2-amino-1-ethylbenzimidazole with benzyl chloride, the monobenzylation product was obtained with a greater yield than the dibenzylamino derivative. Apparently, some difficulty in the introduction of a second benzyl group is connected with its relatively large size in comparison with, for example, methyl or ethyl radicals. However, our results here do not completely agree with the results of the French authors, for whom the yield of tertiary amine in the benzylation of the N-anion of 4-aminoquinoline with benzyl chloride in liquid ammonia was twice the yield of the monobenzyl derivative [5].

TABLE 3. Characteristics of the Dialkylamino Derivatives $RN(Alk)_2$

R	Alk	Bp, °C (nm)	Empirical formula	Found, %			Calculated, %			Picrate, mp, °C (ethanol)
				C	H	N	C	H	N	
α-Pyridyl	C_2H_5	73—75 (5)[9]	$C_9H_{14}N_2 \cdot C_6H_3N_3O_7$	47,6	4,7	18,7	47,5	4,5	18,5	145—146
The same	C_3H_7	104 (7)	$C_{11}H_{18}N_2$	73,9	10,5	15,9	74,1	10,2	15,7	135—136
„ „	C_4H_9	155 (20)[10]	$C_{13}H_{22}N_2$	76,0	10,9	—	75,7	10,7	—	127—129
Isoquinolin-1-yl	C_2H_5	—	$C_{13}H_{16}N_2 \cdot C_6H_3N_3O_7$	52,9	4,0	16,1	53,1	4,3	16,3	151—153
The same	C_3H_7	170 (5)	$C_{15}H_{20}N_2$	79,2	9,2	—	78,9	8,9	—	170—171
„ „	C_4H_9	—	$C_{17}H_{24}N_2 \cdot C_6H_3N_3O_7$	56,7	5,7	14,7	56,9	5,6	14,4	104—105
1-Ethylbenzimidazol-2-yl	C_2H_5	110 (1)[11]	$C_{13}H_{19}N_3$	71,6	9,0	—	71,8	8,8	—	156—158
The same	C_3H_7	—	$C_{15}H_{23}N_3$	73,4	9,8	—	73,4	9,5	—	116—118
„ „	C_4H_9	130 (5)	$C_{17}H_{27}N_3$	74,7	10,1	15,2	74,7	10,0	15,4	125—126

TABLE 4. Characteristics of the Monoalkyl Derivatives RNHAlk

R	Alk	Mp, °C	Bp, °C (nm)	Empirical formula	Found, %			Calculated, %			ν_{NH}, cm^{-1} (par. oil)	Picrate mp, °C (ethanol
					C	H	N	C	H	N		
α-Pyridyl	C_2H_5	—	73—75 (5)[a]	$C_7H_{10}N_2 \cdot C_6H_3N_3O_7$	44,2	3,6	19,7	44,4	3,7	19,9	—	164—165
The same	C_3H_7	—	100 (10)[b]	$C_8H_{12}N_2 \cdot C_6H_3N_3O_7$	46,1	4,1	18,9	46,0	4,2	19,2	—	149—150[13]
„ „	i-C_3H_7	33—34[c]	—	$C_8H_{12}N_2 \cdot C_6H_3N_3O_7$	45,8	4,0	19,1	46,0	4,2	19,2	—	187—188[d]
„ „	C_4H_9	37—39[e]	124—125 (15)[9]	$C_9H_{14}N_2 \cdot C_6H_3N_3O_7$	47,2	4,3	18,0	47,5	4,5	18,0	3263	131—132
Isoquinolin-1-yl	C_2H_5	78—80[f]	—	$C_{11}H_{12}N_2$	76,7	6,8	—	76,7	7,1	—	3290	—
The same	C_3H_7	49—50[f]	—	$C_{12}H_{14}N_2$	77,6	7,6	—	77,4	7,6	—	3280	—
„ „	C_4H_9	40—41[f]	—	$C_{13}H_{16}N_2$	77,9	8,4	—	77,8	8,1	—	3310	175—176
1-Ethylbenzimidazol-2-yl	C_2H_5	163—165[g]	—	$C_{11}H_{15}N_3$	69,7	7,6	—	69,8	7,9	—	3192	—
The same	C_3H_7	134—135[g]	—	$C_{12}H_{17}N_3$	71,3	8,8	—	70,9	8,5	—	3210	—
„ „	C_4H_9	147—148[f]	—	$C_{13}H_{19}N_3$	71,7	8,8	—	71,8	8,8	—	3190	—

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[a] According to [12], bp 79-82°C (4 mm). [b] According to [13], bp 110°C (15 mm). [c] Reprecipitation from hydrochloric acid solution with ammonia. [d] According to [14], picrate with mp 173-175°C. [e] According to [9], mp 40-41°C. [f] Petroleum ether. [g] Toluene.

In agreement with the conclusions of our preceding work, we have found that the N-anions of 2-aminopyridine are alkylated in liquid ammonia considerably more poorly than the N-anions of 4-aminopyridine of the α-amino derivatives of other heterocyclic systems.

On the whole, considering the ease of separation of the secondary and tertiary amines, the alkylation of N-anions with the aid of ethyl and propyl iodides can be recommended as a fairly simple method of obtaining diethylamino and dipropylamino derivatives of N-heterocycles. The properties of the mono- and dialkylamino derivatives of nitrogen heterocycles obtained in this investigation are given in Tables 3 and 4.

EXPERIMENTAL

Ethylation of 4-Aminopyridine. To a suspension of 1.6 g (0.04 mole) of freshly prepared sodium amide in 100 ml of liquid ammonia was added 1.88 g (0.02 mole) of 4-aminopyridine and, after 30 min, in drops, 4.36 g (0.04 mole of ethyl bromide. The mixture was stirred without external cooling and the ammonia was allowed to evaporate off gradually. The residue was extracted with ether (50 ml), and the sodium bromide was filtered off. The ether was distilled off and the oily brownish residue (2.8 g, 92%), consisting of 4-diethylaminopyridine sufficiently pure for synthetic purposes was purified by one of the following two methods:

a) Chromatography on a Column of Alumina. Benzene eluted 2.2 g (73%) of pure 4-diethylaminopyridine. Mp 81-83°C (petroleum ether); according to the literature [7], an oil. Picrate, mp 168-169°C; according to the literature [6] 169-170°C. The PMR and IR spectra (from which the ν_{NH} band was absent) of the compound agreed completely with its structure.

b) Vacuum Distillation. A fraction with bp 146-147°C (18-19 nm) was collected [7]. Yield 2.1 g (69%). The 4-diethylaminopyridine could not always be obtained in the crystalline state.

The alkylation of the amines in the other cases was performed similarly, using for the purification and separation of the alkylation products column chromatography on alumina. Usually, benzene or petroleum ether first eluted the tertiary amine (R_f 0.8-0.9), and then the secondary amine (R_f 0.4-0.5). As an example, the procedure for the reaction of 1-aminoisoquinoline with propyl iodide is given.

Propylation of 1-Aminoisoquinoline. To a suspension of 1.2 g (0.03 mole) of freshly prepared sodium amide in 150 ml of liquid ammonia was added 2.16 g (0.015 mole) of 1-aminoisoquinoline and, after 1.5 h, 5.1 g (0.03 mole) of propyl iodide. The mixture was stirred and the ammonia was allowed to evaporate off slowly. The dry residue was treated with ether (50 ml), and the sodium iodide was separated by filtration. The ether was distilled off and the residue was dissolved in the minimum amount of chloroform and passed through a column of alumina. The 1-dipropylaminoisoquinoline was eluted with petroleum ether, the first fraction being collected. Yield 1.94 g (57%). Then the same eluent eluted 1-propylaminoisoquinoline. Yield 0.55 g (19%).

Benzylation of 2-Amino-1-ethylbenzimidazole. To a suspension of 2.41 g (0.015 mole) of 2-amino-1-ethylbenzimidazole in 150 ml of liquid ammonia was added 0.69 g (0.03 g-atom) of sodium in pieces. The mixture was stirred for 30 min and 3.8 g (0.03 mole) of benzyl chloride was added, after which, with stirring, the ammonia was allowed to evaporate off slowly. The residue was treated with ether (75 ml) and filtered. The ether was distilled off from the filtrate, and the semicrystalline residue (3.1 g) was treated with petroleum ether (100 ml). This extracted 1.5 g (30%) of 2-dibenzylamino-1-ethylbenzimidazole, which formed a viscous light yellow oil. Picrate, mp 197-198°C, which corresponds to the literature figure [8]. The solid residue insoluble in petroleum ether was recrystallized from ethanol, giving 1.44 g (41%) of colorless crystals of 2-benzylamino-1-ethylbenzimidazole with mp 154-155°C, agreeing with the literature [8].

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