IMIDAZOLE DERIVATIVES CONTAINING POTENTIALLY LABILE GROUPINGS ATTACHED TO N_1

VI.* SOME 2-AMINO DERIVATIVES OF 1-ARALKYL- AND 1-METHOXYMETHYLBENZIMIDAZOLES

T. P. Filipskikh, A. F. Pozharskii,
V. N. Koroleva, A. M. Simonov,
and É. A. Zvezdina

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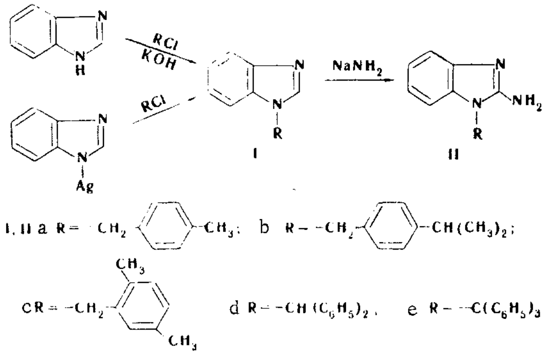
A number of 1-aralkylbenzimidazoles, the amination of which with sodium amide gives 1-aralkyl-2-aminobenzimidazoles, were obtained by the reaction of substituted benzyl chlorides or benzhydryl chlorides with benzimidazole or its silver salt. The successful amination of 1-benzhydrylbenzimidazole attests to the insignificant influence of steric effects on the Chichibabin reaction in the benzimidazole series [2]. 1-Methoxymethyl-2-aminobenzimidazole was obtained by the reaction of methoxymethyl chloride with the sodium salt of 2-aminobenzimidazole in absolute dioxane.

We needed a series of 1-aralkyl-2-aminobenzimidazoles (II) and 1-methoxymethyl-2-aminobenzimidazole (IV) for the generation of the highly reactive 2-aminobenzimidazole anions by the reductive cleavage of the N–R bond with sodium in liquid ammonia.



With this end in mind, we subjected benzimidazole to the action of a number of substituted benzyl chlorides in alcoholic alkali, as a result of which we obtained good yields of 1-aralkylbenzimidazoles (Ia-c). 1-Benzhydrylbenzimidazole (Id) is best obtained by the reaction of the silver salt of benzimidazole with benzhydryl chloride, the use of which gives higher and more reproducible yields than benzhydryl bromide [4].

Compounds I readily form the corresponding 2-amino derivatives (IIa-d) on reaction with sodium amide in absolute dimethylaniline.

We were unable to obtain 1-trityl-2-aminobenzimidazole (IIe) by either amination of 1-tritylbenzimidazole [5] or by the reaction of trityl chloride with the sodium salt of 2-aminobenzimidazole in absolute xylene. In both cases, the starting compound and triphenylcarbinol were isolated from the reaction mixture.

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*See [1] for communication V.

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TABLE 1. Characteristics of the Synthesized Compounds

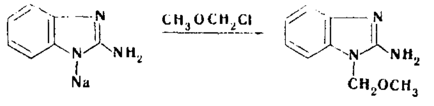
Compound	mp, °C[a]	IR spectrum (mineral oil), cm^{-1}[c]		Empirical formula	Found, %			Calc., %			Yield, %
		ν_{as}	ν_s		C	H	N	C	H	N	
Ia	156[b]	—	—	$C_{15}H_{14}N_2 \cdot C_6H_3N_3O_7$	56,0	3,8	15,6	55,9	3,8	15,5	57
Ib	163—164	—	—	$C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$	57,4	4,4	14,7	57,6	4,4	14,6	70
Ic	165—166	—	—	$C_{16}H_{16}N_2 \cdot C_6H_3N_3O_7$	56,7	4,2	15,2	56,8	4,1	15,1	60
Id	161	—	—	$C_{20}H_{16}N_2$	84,4	5,7	9,7	84,5	5,7	9,9	53
IIa	175—176	3440	3350	$C_{15}H_{15}N_3$	75,8	6,5	17,5	75,9	6,4	17,7	72
IIb	200—201	3480	3400	$C_{17}H_{19}N_3$	76,8	7,2	15,7	76,9	7,2	15,8	63
IIc	192—193	3455	3316	$C_{16}H_{17}N_3$	76,5	7,0	16,9	76,5	6,8	16,7	61
IId	217—218	3444	3290	$C_{20}H_{17}N_3$	79,8	5,6	14,3	80,3	5,7	14,0	54
IV	147—148	—	—	$C_9H_{11}N_3O$	60,9	6,0	—	61,0	6,3	—	80

[a] Compound Ia was recrystallized from acetic acid, Ib, c were recrystallized from alcohol, Id was recrystallized from aqueous alcohol, IIa-d were recrystallized from benzene, and IV was recrystallized from water.

[b] The boiling points of bases Ia-c were 150° (10 mm), 140-145° (7 mm), and 200° (80 mm), respectively.

[c] For ν_{NH_2}.

In addition, IV, which cannot be obtained by direct amination of 1-methoxymethylbenzimidazole [6], is formed in good yield in the reaction of methoxymethyl chloride with the sodium salt of 2-aminobenzimidazole (III).



III IV

EXPERIMENTAL

1-Benzyhydrylbenzimidazole (Id). A 16.3-g (0.08 mole) sample of freshly prepared benzhydryl chloride was added to a suspension of 18.1 g (0.08 mole) of the finely ground silver salt of benzimidazole in 140 ml of absolute xylene, and the mixture was refluxed with stirring and isolating from light for 3 h. The hot solution was filtered, and the AgCl was washed on the filter with hot xylene. The xylene was removed from the filtrate by distillation, and the residual oil began to crystallize very rapidly. The solid mass was triturated with ether, and the mixture was filtered to give 53% of crude product. This was crystallized from aqueous alcohol to give colorless crystals with mp 161° (162-163° [3]).

1-(p-Methylbenzyl)benzimidazole (Ia). A solution of 11.8 g (0.01 mole) of benzimidazole in 60 ml of alcoholic potassium hydroxide [7.84 g (0.14 mole)] was refluxed with stirring with 19.3 g (0.14 mole) of p-xylyl chloride for 5 h. The precipitated KCl was removed by filtration, and washed with chloroform. The solvent was removed by distillation, and the resulting oil was extracted with chloroform. The chloroform extract was washed with 10% NaOH solution and dried with potassium carbonate. The solvent was removed by distillation, and the residue was vacuum-distilled to give 12 g (57%) of a light-yellow oil with bp 150° (10 mm). Compounds Ib, c were similarly obtained.

1-Benzhydryl-2-aminobenzimidazole (IId). A solution of 8 g (0.028 mole) of Id in 40 ml of absolute dimethylaniline was slowly added dropwise to a suspension of 5.5 (0.14 mole) of sodium amide in 15 ml of absolute dimethylaniline, heated to 110°, at a rate sufficient to ensure uniform hydrogen evolution (~ 1 h). The mixture was stirred at 140° for 1 h, cooled, and treated with 40 ml of water. The precipitated amine crystals were removed by filtration. A large portion of the amine was isolated from the filtrate when the dimethylaniline was removed by steam distillation. The residual oil began to crystallize on cooling. The crystals were removed by filtration and washed with water, petroleum ether, and ether to give an overall yield of 4.6 g (54%) of colorless crystals with mp 217-218° (benzene).

Compounds IIa-c were similarly obtained. IR spectra of IIa-d, cm^{-1}: ν_{as} 3440, 3480, 3455, and 3444 (respectively); ν_s 3350, 3400, 3316, and 3290.

1-Methoxymethyl-2-aminobenzimidazole (IV). A 2-g (0.015 mole) sample of 2-aminobenzimidazole was refluxed under nitrogen with 0.9 g (0.023 mole) of sodium amide in 20 ml of absolute dioxane for 2 h. The mixture was then cooled while maintaining the passage of nitrogen, 1.32 g (0.015 mole) of methoxymethyl chloride was added, and the mixture was refluxed for 2 h. It was then cooled, and the precipitated NaCl was removed by filtration and washed with benzene. The benzene was removed by distillation to give 0.24 g of product. The dioxane was removed by distillation to give another 2.57 g of product for an overall yield of 80% of a compound with mp 147-148° (water).

The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrophotometer.

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