IMIDAZOLE DERIVATIVES CONTAINING POTENTIALLY LABILE GROUPINGS ATTACHED TO AN N-ATOM

V. Synthesis of 2-Benzylamino- and 2-Dibenzylaminobenzimidazoles*

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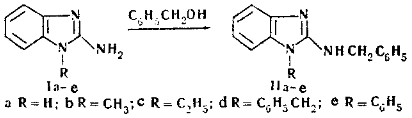
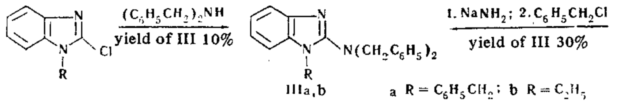
The action of benzyl alcohol on 2-aminobenzimidazoles in the presence of alkali has given a high yield of a number of 2-benzylaminobenzimidazoles which have been converted subsequently into 2-dibenzylaminobenzimidazoles and 2-benzyliminobenzimidazolines.

2- Benzylaminobenzimidazoles II offer interest as starting materials for the generation of highly reactive N-anions of 2-aminobenzimidazole [2]. We have established that II, like 2-benzylaminopyridine [3], can easily be obtained by reacting the corresponding amines I with benzyl alcohol in the presence of alkali. The yields of II are close to quantitative. The benzylation of unsubstituted 2-aminobenzimidazole takes place less readily and in lower yield.



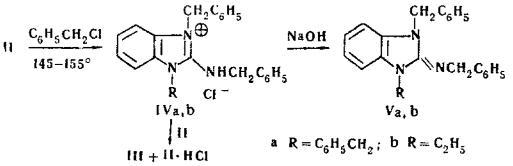
Compound IIa was also obtained with a yield of 70% by the debenzylation of IId with 2 g-at. of sodium in liquid ammonia.

We have synthesized 2-dibenzylaminobenzimidazoles (III) by two methods.



In the reaction of 2-chlorobenzimidazoles with dibenzylamine, the yield of III was only 10%. In this reaction, the evolution of a large amount of tribenzylamine was observed, but we did not study the mechanism of its formation. The synthesis of III by the benzylation of the sodium salts of compounds II with benzyl chloride in toluene gave somewhat better results. The formation of 2-dibenzylaminobenzimidazoles as by-products (yield 12-15%) was not expected in the benzylation of the bases II with benzyl chloride in xylene or cumene. As expected, the main products of this reaction are the 2-benzyliminobenzimidazolines V (yield 51–55%).

As we established in a specially performed experiment, the formation of compounds III results from the intermolecular transfer of the benzyl radical from the quaternary salt IV to the exocyclic amino group of the initial compound II, which takes place at an elevated temperature.



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*For part IV, see [1].

We established the structures of the isomeric compounds **III** and **V** on the basis of an analysis of their UV absorption spectra. The amines **III** showed two maxima on the absorption curve in the 252–254- and 284–288-nm regions, while the imines have only one maximum, at 284–288 nm, and a characteristic minimum at 255 nm (see [6]).

Compounds Synthesized*

Compound	Mp, °C	Solvent for crystallization	Empirical Formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIa	161—162	Benzene	$C_{14}H_{13}N_3$	75,06	6,04	18,45	75,31	5,87	18,82	50—70
IIb	167	Methanol	$C_{15}H_{15}N_3$	75,88	6,31	17,92	75,94	6,36	17,70	Quantitative
IIc	155—156	Ethanol	$C_{16}H_{17}N_3$	76,72	6,79	16,86	76,46	6,82	16,72	Quantitative
IId	121—122	Acetone-water	$C_{21}H_{19}N_3$	80,44	6,07	13,70	80,48	6,11	13,41	91
IIe	145	Ethanol	$C_{20}H_{17}N_3$	80,57	5,99	14,27	80,23	5,73	14,04	Quantitative
IIIa	101—102	Heptane	$C_{28}H_{25}N_3$	83,00	6,24	10,71	83,34	6,25	10,41	10—30
IIIb	oil	—	$C_{23}H_{23}N_3$**	—	—	—	80,90	6,79	12,31	31
Va	101—102	Ethanol	$C_{28}H_{25}N_3$	83,24	6,31	10,76	83,34	6,25	10,41	55
Vb	oil	—	$C_{23}H_{23}N_3$	80,44	6,84	12,71	80,90	6,79	12,31	51

*Compounds IIb and IIe have been obtained previously by a complicated route and in low yield [4,5].

**The compound was subjected to analysis in the form of the picrate (see experimental section).

EXPERIMENTAL

2-Benzylamino-1-methylbenzimidazole (IIb). A mixture of 1.47 g (0.01 mole) of 2-amino-1-methylbenzimidazole, 1.62 g (0.015 mole) of benzyl alcohol, and 0.09 g of caustic potash was heated with a Bunsen burner. At ~150° C (thermometer immersed in the reaction mixture), the mixture effervesced vigorously. The temperature was gradually raised to 250° C and kept there for 5 min, after which the mixture was cooled to about 100–150° C, then water was added carefully with stirring. The precipitate was filtered off and washed with water and a small amount of ether, and was dried in the vacuum desiccator over P_2O_5. Colorless crystals with mp 167° C (from methanol). Yield quantitative.

Compounds **IIc–d** were obtained similarly (see table).

2-Benzylaminobenzimidazole (IIa). A) This was obtained by the method described above except that the mixture was kept at 250° C for ~2 hr. The unchanged 2-aminobenzimidazole was washed out with hot water.

B) In small pieces, 0.7 g (30 mg-at.) of sodium was added to a suspension of 1.57 g (5 mM) of 1-benzyl-2-benzylaminobenzimidazole in 50 ml of liquid ammonia. The mixture was stirred at -75° C for half an hour, and then 1.6 g (30 mM) of ammonium chloride was added. After the evaporation of the ammonia, the dry residue was treated with ethyl acetate (75 ml). The ethyl acetate was distilled off and the 2-benzylaminobenzimidazole obtained was washed free from the by-product 2-aminobenzimidazole (0.2 g) with hot water. The yield of **IIa** (see table) was 0.78 g (70%).

2-Dibenzylamino-1-benzylbenzimidazole (IIIa). A) mixture of 0.88 g (3.6 mM) of 1-benzyl-2-chlorobenzimidazole [7] and 1.42 g (7.2 mM) of freshly distilled dibenzylamine was stirred at 170–190° C for 10 hr. After cooling, the light brown melt was treated with benzene (20 ml), and the residue (0.9 g), consisting of dibenzylamine hydrochloride, was filtered off and washed with benzene and ether. The filtrate, after the benzene had been driven off, yielded 1.3 g of a brown caramellike mass from which compound **IIIa** was isolated by chromatography on a column of alumina. First, petroleum ether eluted 0.85 g (43%) of tribenzylamine with mp 91° C (according to the literature [8], mp 92° C). Then a mixture of petroleum ether and ether (5 : 1) eluted **IIIa**. Yield 0.15 g (10%). Colorless needles (from heptane), mp 101–102° C. UV spectrum (in methanol): λ_{max} 252, 285 nm; log ε 3.99, 4.03.

B) A mixture of 1.57 g (5 mM) of 1-benzyl-2-benzylaminobenzimidazole, 0.98 g (25 mM) of ground sodium amide, and 10 ml of absolute toluene was boiling with stirring in a current of dry nitrogen for 2 hr. The resulting suspension of the sodium derivative was treated with 0.62 g (5 mM) of benzyl chloride. The mixture was heated for 1 hr and filtered, and the filtrate was evaporated to give 2 g of a light-brown oil containing **IIIa** together with the starting material. The mixture of these substances was separated chromatographically as a method A. Yield 0.6 g (30%).

2-Dibenzylamino-1-ethylbenzimidazole (IIIb). This was obtained and isolated in a manner similar to **IIIa** [method B]. Yield 31%. Very viscous yellow oil. UV spectrum (in methanol): λ_{max} 255, 286 nm; log ε 3.70, 3.81.

Picrate, Mp 197–198° C (from ethanol). Found, %: N 14.61. Calculated for $C_{23}H_{23}N_3 \cdot C_6H_3N_3O_7$, %: N 14.73.

1,3-Dibenzyl-2-benzyliminobenzimidazoline (Va). A solution of 3.13 g (0.01 mole) of **IId** and 3 ml (0.025 mole) of benzyl chloride in 20 ml of cumene was boiled for 10 hr. After cooling, the precipitate was filtered off and washed with benzene and ether, after which it was dissolved in ethanol and treated with alkali. This gave colorless crystals of **Va** with mp 101–102° C (from ethanol). Yield 2.25 g (55%). UV spectrum (in methanol): λ_{max} 286 nm; log ε 4.10. **Hydrochloride,** Mp 238–239° C (from ethanol). From the brown residue obtained after the distillation of the cumene 0.6 g (15%) of 2-dibenzylamino-1-benzyl-benzimidazole was isolated chromatographically as described above. A mixture with an authentic sample gave no depression of the melting point (101–102° C), while with the imine **Va** a considerable depression was observed.

3-Benzyl-2-benzylimino-1-ethylbenzimidazoline (Vb). This was obtained in a manner similar to **Va.** Yellowish oil which was purified chromatographically (Al_2O_3 with petroleum ether as eluent) or via the hydrochloride [mp 222–223° C (from ethanol with the addition of ether)]. UV spectrum (in methanol): λ_{max} 286 nm; log ε 3.92. Compound **IIIb** was obtained as a by-product (yield 12%) (see table).

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