BRIEF COMMUNICATIONS

IMIDAZOLE DERIVATIVES CONTAINING POTENTIAL LABILE GROUPINGS ON A NITROGEN ATOM

II. Synthesis and Properties of N-Mercaptoalkylbenzimidazoles*

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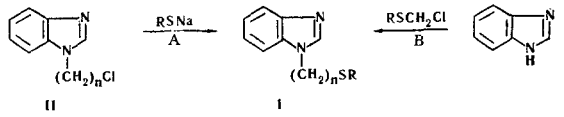
A number of N-mercaptomethyl- and N-(β-mercaptoethyl)benzimidazoles has been synthesized and their properties have been studied.

In recent years, attention has been devoted to 2-mercaptoalkylbenzimidazoles in connection with their possible pharmacological activity [2, 3]. However, the N-mercaptoalkylbenzimidazoles isomeric with them have not hitherto been known. We have synthesized a number of compounds of this type and have studied the possibility of using the mercaptoalkyl groups as N-imidazole protection.

We obtained the N-mercaptoalkylbenzimidazoles (I) by two methods: starting from N-chloroalkylbenzimidazoles (II) and mercaptans in an alkaline medium (A), and by alkylating benzimidazole with alkyl chloromethyl sulfides (B).



II I

a n=1, R=n-C_4H_9; b n=1, R=$C_6H_5CH_2$; c n=1, R=C_6H_5; d n=1, R=purin-6-yl; e n=2, R=purin-6-yl; f n=2, R=n C_4H_9; g n=2, R=C_6H_5

Both variants give good results, and the yields amount to 70–80%. In the N-mercaptomethylbenzimidazoles (Ia–Id), the mercaptomethyl group is distinguished by considerable lability: benzimidazole appears in the solution after only an hour on boiling in water, and immediately with 6 N hydrochloric acid. Dilute solutions of alkali do not decompose Ia–Id in the cold. In contrast to their nitrogen analogs, the N-(aminomethyl)benzimidazoles [1], compounds I form completely stable hydrochlorides and picrates. Thus, the lability of the groups in the N-substituted benzimidazoles that we have studied [1] fall in the sequence $-CH_2NR_2 > CH_2SR > CH_2OR$. Because of the high mobility of the $-CH_2NR_2$ group and, to some extent, of the $-CH_2SR$ group, their use as N-imidazole protection is hardly desirable. Far more promising for these purposes is the alkoxymethyl protection $-CH_2OR$, which we shall study in more detail subsequently.

As was to be expected, the N-mercaptoethylbenzimidazoles Ie–Ig proved to be completely stable substances resisting hydrolytic decomposition in all media.

Compounds Id and Ie, obtained from 6-mercaptopurine and containing a purin-6-yl residue present particular pharmacological interest. Compound Id, like the other compounds I (n = 1) proved to be fairly unstable, decomposing partially even on crystallization. In contrast, Ie is a completely stable compound.

The reaction of compounds I with sodium amide has been described previously [4].

EXPERIMENTAL

The two general methods of obtaining N-mercaptoalkylbenzimidazoles are described below. All the compounds I were obtained by method A. Compounds Ia and Ib were also synthesized by method B.

A) To a solution of 0.01 mole of 1-chloromethyl- or 1-(β-chloroethyl)-benzimidazole [1, 4] in ethanol was added 0.1 mole of the appropriate mercaptan and then an ethanolic solution of 0.02 mole of caustic soda. The mixture was boiled in a current of nitrogen for 2 hr,

*For part I, see [1].

Characteristics of the N-Mercaptoalkylbenzimidazoles

Mp, °C	Empirical formula	Found, %					Calculated, %				Yield, %	Mp of the picrate, °C
			C	H	N	S	C	H	N	S		
Ia		$C_{12}H_{16}N_2S$	—	—	12.92	14.67	—	—	12.72	14.55		163[d]
Ib	83.5—84.5[a]	$C_{15}H_{14}N_2S$	70.74	5.82	10.72	12.37	70.84	5.55	11.01	12.60		197[e]
Ic	89—90[a]	$C_{14}H_{12}N_2S$	70.05	4.97	11.79	12.82	69.97	5.03	11.66	13.34		151[d]
Id	221 b	$C_{12}H_{10}N_6S$	—	—	29.28	11.01	—	—	29.77	11.36		—
Ie	211 c	$C_{14}H_{12}N_6S$	56.75	4.13	28.79	10.36	56.74	4.08	28.36	10.82		—
If		$C_{13}H_{18}N_2S$	—	—	12.31	13.49	—	—	11.96	13.68		125[f]
Ig		$C_{15}H_{14}N_2S$	70.66	5.46	11.38	12.35	70.84	5.55	11.01	12.60		133[d]

Solvent for crystallization: [a]petroleum ether (bp 86–92° C); [b]toluene; [c]water; [d]ethanol; [e]ethanol–acetone; [f]glacial acetic acid.

and then the precipitate of sodium chloride was filtered off and the ethanol was distilled off from the filtrate. The oily residue was treated with alkali and was then dissolved in chloroform and passed through a column of Al_2O_3. Compounds **Ib–Ie**, which were not passed through the column, were additionally recrystallized (see table). Because of the decomposition and oxidation of compounds I on vacuum distillation, we limited ourselves to the chromatographic purification of the oily compounds **Ia**, **If**, and **Ig**.

B) A mixture of 0.02 mole of benzimidazole and 0.01 mole of the corresponding alkyl chloromethyl sulfide in 30 ml of absolute benzene was boiled for 3 hr. The precipitate of benzimidazole hydrochloride that had deposited was filtered off, and the benzene was distilled off from the filtrate. The residual oil was purified as described above.

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SYNTHESIS OF 1,4-DIARYL-2,5-DIOXOPIPERAZINES

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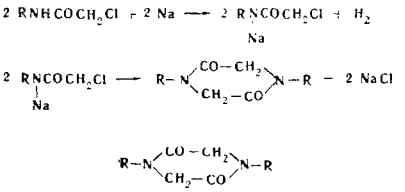
A new method for the synthesis of 1,4-diaryl-2,5-dioxopiperazines by the condensation of chloroacetanilides in the presence of sodium in anhydrous solvents, has been developed. The evolution of hydrogen shows the nucleophilic nature of the condensation.

Dioxopiperazines have been the subject of numerous investigations because of their relationship with the amino acids and peptides. The synthetic methods for obtaining dioxopiperazines consist in fusing amino acids and their derivatives in a current of inert gas or in solvents [1].

1,4-Diaryl-2,5-dioxopiperazines have been obtained [2] by the brief action of alcoholic alkalies on chloroacetyl derivatives. However, this synthesis is accompanied by side reactions which complicate the isolation of the end products. In recent years, it has been shown that the condensation of α-chloroacetamides also takes place under the action of sodium amide in liquid ammonia [3].

In attempting to develop the synthetic limits to the use of α-chloroacetamides, we have found a simpler



R	Mp, °C	Empirical formula	IR spectra, cm^{-1}					Found, %			Calculated, %			Yield, %
				C_{ar}—N	C—N—C_{ar}	>C=O	CH_2	C	H	N	C	H	N	
C_6H_5	262—263	$C_{16}H_{14}O_2N_2$	1600	1258	1440	1665—1675	1457	72.20	5.83	10.20	72.18	5.26	10.50	57
p-$CH_3C_6H_4$	252—253	$C_{18}H_{18}O_2N_2$	1520	1258	1437	1665—1675	1473	73.31	5.85	9.72	73.40	6.12	9.52	49
p-$CH_3OC_6H_4$	257—258	$C_{18}H_{18}O_4N_2$	1520	1252	1472	1665—1675	1472	66.57	5.78	8.55	66.27	5.52	8.58	62
p-$C_2H_5OC_6H_4$	266—267	$C_{20}H_{22}O_4N_2$	1590	1250	—	1665—1675	1480	68.00	6.56	8.25	67.80	6.21	7.91	41
β-$C_{10}H_7$	313—314	$C_{24}H_{18}O_2N_2$	1607	1278	1445	1665—1675	1470	78.65	5.31	8.00	78.68	4.92	7.65	57