

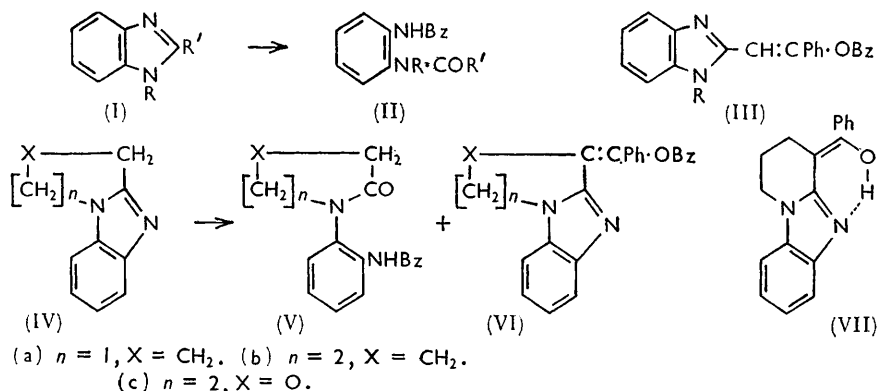
1004. *Acylation of Benzimidazoles.*

By O. METH-COHN.

Benzoylation of 1,2-disubstituted benzimidazoles (IV) gives rise to both *N*-benzoylated and *C*-benzoylated products. A mechanism for this reaction is proposed and shown to involve an enamine intermediate.

TREATMENT of 1,2-disubstituted benzimidazoles (I) with an excess of benzoyl chloride in dilute sodium hydroxide solution gives *o*-phenylenediamine derivatives (II).<sup>1</sup> However, when a methyl or methylene group is present in the 2-position of the benzimidazole ring, a second product is also obtained. Thus, 2-methyl-1-phenylbenzimidazole (I; R = Ph, R' = Me) gives both the *N*-benzoylated derivative (II; R = Ph, R' = Me) and the *C*-benzoylated product (III; R = Ph).<sup>1</sup> Similarly, we obtained the analogous products (V) and (VI) from the tricyclic benzimidazoles (IVa, b, and c).

Wolff<sup>1</sup> reported that hydrolysis of the enol ester (III) with ethanol or aqueous hydrochloric acid yielded 2-phenacyl-1-phenylbenzimidazole (I; R = Ph, R' = CH<sub>2</sub>Bz), which gave the usual ketonic reactions and derivatives as well as a green colour with ferric chloride, indicating the presence of enol form of the product. The corresponding hydrolysis product (VII) from one of our benzimidazoles (IV; n = 2, X = CH<sub>2</sub>), however, showed no ketonic reactions and no carbonyl peak in the infrared spectrum, but gave an intense green colour with ferric chloride. It is likely that intramolecular hydrogen bonding, together with the 1,2-ring in the benzimidazole structure (VII), renders the enolic form more stable than in



Wolff's series, in which the 1,2-ring is not present. However, when either the enol esters (VI) or the enols of type (VII) were boiled with ethanolic sodium hydroxide, the parent benzimidazoles (IV) were recovered. In alkaline solution, therefore, the stabilising influence of the "enol ring" is lost, facilitating the removal of the benzoyl moiety in a manner analogous to the "acid hydrolysis" of acetoacetic ester systems.

Hydrolysis of the ring-opened derivatives (V) with aqueous sulphuric acid or ethanolic sodium hydroxide gave the parent benzimidazoles (IV), suggesting that removal of the benzoyl group occurs first, followed by the catalysed removal of the elements of water, comparable with the Phillips benzimidazole reaction.<sup>2</sup>

The mechanism of the conversion of the benzimidazoles (IVa, b, and c) into the ring-opened compounds (Va, b, and c) has been clearly shown to involve the acylbenzimidazolium hydroxide (1) and the "pseudo-base" (2).<sup>1,3-5</sup> However, the mode of formation

<sup>1</sup> Wolff, *Annalen*, 1913, **399**, 297.

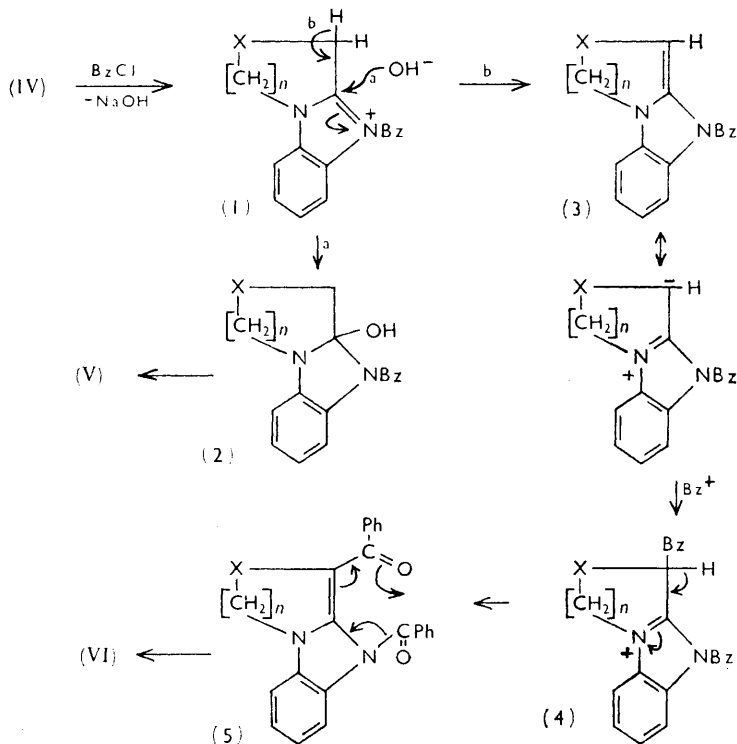
<sup>2</sup> Phillips, *J.*, 1928, 2395.

<sup>3</sup> Gerngross, *Ber.*, 1913, **46**, 1908, 1913.

<sup>4</sup> Bamberger and Berlé, *Annalen*, 1893, **273**, 342.

<sup>5</sup> Oddo and Raffa, *Gazzetta*, 1937, **67**, 537; 1938, **68**, 199.

of the enol esters (VI) has not been satisfactorily explained. The reaction can be considered to result from the formation of the enamine (3) by an *E2*-type elimination. Benzoylation of the enamine would then give the dibenzoylated compound (4). When the benzoylation was carried out in dry pyridine instead of aqueous sodium hydroxide, the enol esters were formed exclusively, suggesting that under hydroxylic conditions the acylated benzimidazole (1) is converted competitively into either the enamine (3) or the pseudobase (2). The enol esters (VI) result by the indicated cyclic rearrangement [(5)  $\rightarrow$  (VI)],



the consequent aromatisation and extended conjugation conferred on the product being the driving force.

It is noteworthy in this connection that enamines have actually been isolated in the 2-methylbenzothiazole series by treatment of the methiodide with sodium hydroxide.<sup>6-9</sup> A number of reactions of these compounds (referred to as "methylene bases" in the literature) with electrophilic reagents (including acylations in pyridine) have been reported.<sup>10,11</sup> Formation of cyanine dyes and related compounds from 2-methylbenzothiazole and 2-methylbenzoxazole methiodides probably proceed by way of the corresponding enamines.<sup>10</sup>

In order to "trap" the dibenzoylated product (5), the benzimidazole (IVb) was reacted with phthaloyl chloride in pyridine, with a view to forming a diacylated product in which both acyl groups were attached to the same ring, hence stabilising the intermediate. The yellow product (VIII) so obtained gave analysis figures expected for the comparable intermediate to (5), but showed no ketonic reactions, a green ferric chloride coloration

<sup>6</sup> König and Meier, *J. prakt. Chem.*, 1925, [2], **109**, 324.

<sup>7</sup> Clark, *J.*, 1928, **2313**.

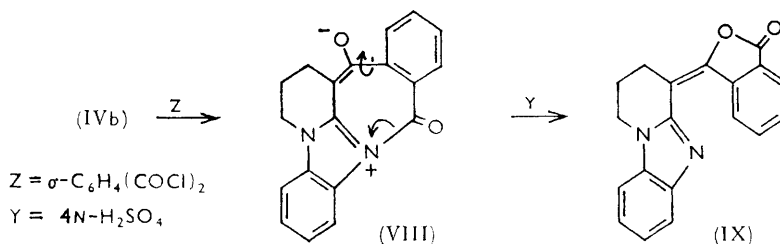
<sup>8</sup> Mumm, Hinz, and Diederichsen, *Ber.*, 1939, **72**, 2107.

<sup>9</sup> Hamer, Rathbone, and Winter, *J.*, 1947, 954.

<sup>10</sup> Roberts, *Chem. and Ind.*, 1947, 658, and references cited therein.

<sup>11</sup> Brooker, Dent, Heseltine, and Van Lare, *J. Amer. Chem. Soc.*, 1953, **75**, 4335.

and only one carbonyl peak in the infrared spectrum,  $\nu_{\max}$ . (Nujol)  $1675 \text{ cm.}^{-1}$  (amide C:O). These facts may be explained by the structure (VIII), which could give rise to other resonance forms. When this compound is boiled in 4*N*-sulphuric acid for 1 hour, the analogous conversion into the enol ester [(5)  $\rightarrow$  (VI)] occurs to give the isophthalone



(IX). This product no longer gives an enol colouration with ferric chloride, but fluoresces in solution, and gives a lactone carbonyl peak in the infrared spectrum ( $1770 \text{ cm.}^{-1}$ ).

### EXPERIMENTAL

Light petroleum had boiling point  $100\text{--}120^\circ$ .

*Benzimidazoles.*—The preparation of these compounds is described elsewhere.<sup>12</sup>

*Acylation.*—The benzimidazoles were acylated by one of the following methods, the results being summarised in Table 1. (a) The benzimidazole (2 g.) was vigorously shaken with benzoyl

#### Acylated benzimidazoles.

Compound	Method	M. p.	Solvent *	Found (%)			Formula	Required (%)			Remarks
				C	H	N		C	H	N	
(Va)	a	139°	A	72.9	5.8	—	$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$	72.85	5.8	—	Plates
(Vb)	a	147	B	74.0	5.9	9.2	$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$	73.5	6.2	9.5	Prisms
(Vc)	a	150	B	68.5	5.5	9.6	$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$	68.9	5.4	9.5	Needles
(VIa)	a, b	231	C	78.3	5.0	—	$\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_2$	78.7	5.0	—	Needles
(VIb)	a, b	185—186	C	78.6	5.1	7.6	$\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_2$	78.95	5.3	7.4	Needles
(VIc)	a, b	158—159	D	75.3	4.6	7.0	$\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_2$	75.4	4.75	7.3	Needles
(VIII)	b	178—179	E	75.5	4.7	9.5	$\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2$	75.5	4.7	9.3	Yellow needles

\* A, Benzene–light petroleum; B, light petroleum; C, aqueous dioxan; D, ethyl acetate–light petroleum; E, aqueous ethanol.

chloride (5 ml.) in a mixture of aqueous sodium hydroxide (15%; 20 ml.) and ether (10 ml.) for 10 min. Any precipitated material (VI) was filtered off and the ether solution was washed, dried, and evaporated. The *N*-benzoylated product (V) was extracted with hot light petroleum, leaving a further amount of the enol ester.

(b) To the benzimidazole (2 g.) in pyridine (15 ml.) was added the acid chloride (5 ml.), and the mixture heated on a water-bath for 15 min. On pouring into iced water, the precipitated oily product crystallised and, after filtering, was purified by crystallisation.

*Hydrolyses of Acylated Benzimidazoles.*—The acylated benzimidazole (V–IX) was refluxed with aqueous sulphuric acid (4*N*) or ethanolic sodium hydroxide (N) for 2 hr. Alkaline hydrolysis afforded the parent benzimidazole (IV) in every case. Acid hydrolysis of the *N*-benzoylated products (VI) afforded the enol (VII) as needles, m. p.  $169\text{--}170^\circ$  (from ethanol) (Found: C, 77.2; H, 6.2.  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$  requires C, 77.65; H, 6.6%).

The phthaloylated benzimidazole (VIII) gave, on acid hydrolysis, the *isophthalone* (IX) as lemon-yellow needles, m. p.  $274^\circ$  (from ethylene glycol dimethyl ether) (Found: C, 75.4; H, 4.8.  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}_2$  requires C, 75.5; H, 4.7%).

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