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RESEARCH ON THE CHEMISTRY OF 2-HETARYLBENZIMIDAZOLES.

5.* ACYLATION OF 1-METHYL-2-(2'-HETARYL)BENZIMIDAZOLES

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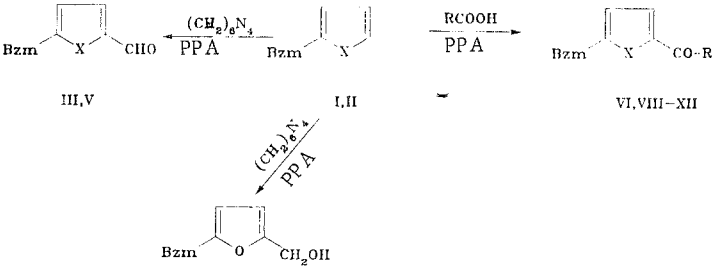
The acylation of 1-methyl-2-(2'-furyl)- and 1-methyl-2-(2'-thienyl)benzimidazoles was studied. A convenient method for the formylation of the furan and thiophene rings by the action of urotropin in polyphosphoric acid (PPA) was found. Acylation of the furan and thiophene rings was realized by the action of acetic acid and aromatic carboxylic acids in PPA.

It has been previously shown [2] that, despite the acidophobic properties of the furan ring, electrophilic-substitution reactions in 1-methyl-2-(2'-furyl)benzimidazole proceed smoothly to give the products in high yields even under rather severe conditions. It seemed of interest to study the behavior of 1-methyl-2-(2-furyl)- (I) and 1-methyl-2-(2-thienyl)-benzimidazole (II) in reactions with weaker electrophilic reagents.

The formylation of five-membered heterocycles and their derivatives has been realized by the Vilsmeier reaction [3, 4]. We attempted to introduce a formyl group by means of this reaction into I and II by the action of the dimethylformamide (DMF)—$POCl_3$ complex. However, the compounds proved to be inert, and we therefore used formylation with urotropin in polyphosphoric acid (PPA) [5].

Compound I forms a 5'-formyl-substituted derivative (III) in no higher than 31% yield. In addition, 5'-hydroxymethyl derivative IV was also obtained in 49% yield. In contrast to I, II forms 1-methyl-2-(5'-formyl-2'-thienyl)benzimidazole (V) smoothly and in high yield.



I X=O; II X=S; III X=O; V X=S; VI X=O, R=CH_3; VIII X=S, R=CH_3; IX, X X=O, S, R=C_6H_5; XI, XII X=O, S; R=*o*-Cl—C_6H_4; 1-methyl-2-benzimidazolyl

*See [1] for communication 4.

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TABLE 1. 1-Methyl-2-(5'-acyl-2'-hetaryl)benzimidazoles (III, V-VI, and VIII-XII)

Compound	mp, °C (from alcohol)	IR spectrum, cm⁻¹ (CO)	Reaction time, h	Found, %			Empirical formula	Calc., %			Yield, %
				C	H	N		C	H	N	
III	148—149 [1]	1680	1	—	—	—	$C_{13}H_{10}N_2O_2$	—	—	—	31
V	134—135 [1]	1680	10	—	—	—	$C_{13}H_{10}N_2OS$	—	—	—	91
VI	135—136	1670	6	69,6	5,2	11,8	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	52
VIII	160—161	1680	20	65,2	4,6	11,2	$C_{14}H_{12}N_2OS$	65,6	4,7	10,9	22
IX	150—151 [9]	1680	10	—	—	—	$C_{19}H_{14}N_2O_2$	—	—	—	72
X	179—180	1660	20	71,4	4,3	9,0	$C_{19}H_{14}N_2OS$	71,7	4,4	8,8	47
XI	145—146	1680	5	68,0	3,5	8,4	$C_{19}H_{13}ClN_2O_2$	67,8	3,9	8,3	72
XII	147—148	1680	20	64,3	3,9	7,9	$C_{19}H_{13}ClN_2OS$	64,7	3,7	7,9	51

TABLE 2. PMR Spectra of Hetarylbenzimidazoles

Compound	Chemical shifts, δ, ppm (CF_3COOH)
III	3,9 (s, 3H, N—CH_3); 7,0 (d, 1H, 4'-H); 7,3 (d, 1H, 3'-H); 7,4 (m, 4H arom); 9,65 (s, 1H, CHO)
IV	3,9 (s, 3H, N—CH_3); 4,6 (s, 2H, CH_2); 5,2 (s, 1H, OH); 6,5 (d, 1H, 4-H); 7,2 (d, 1H, 3-H'); 7,4 (m, 4H arom.)
V	3,9 (s, 3H, N—CH_3); 7,4 (m, 4H, arom.); 7,7 (d, 1H, 4-H); 7,8 (d, 1H, H'$_3$); 9,7 (s, 1H, CHO)
VI	3,9 (s, 3H, N—CH_3); 2,3 (s, 3H, $COCH_3$); 7,2 (d, 1H, 4'-H); 7,4 (m, 4H, arom)
VIII	3,8 (s, 3H, N—CH_3); 7,8 (d, 1H, 3'-H); 7,65 (d, 1H, 4'-H); 2,33 (s, 3H, $COCH_3$); 7,4 (m, 4H, arom.)

In addition to signals of an N-methyl group and a multiplet of aromatic protons, the PMR spectrum of V contains two doublets at 7.6 and 7.8 ppm, which belong to the 4'-H and 3'-H protons, and a singlet at 9.7 ppm, which is characteristic for the CHO proton.

We were unable to obtain acyl derivatives of I and II by means of the Friedel—Crafts reaction with the aid of various catalysts [$AlCl_3$, $ZnCl_2$, $SnCl_4$, BF_4, $HClO_4$, $Mg(ClO_4)_2$]. We therefore used acetylation of phenols and phenyl ethers with acetic acid or its anhydride, which was proposed by Gardner [6]. The reaction was carried out in PPA, which serves simultaneously as the solvent and the catalyst. Compound I was acetylated by the action of acetic acid (the product was obtained in 52% yield); the acyl group was incorporated in the 5' position of the furan ring. A side product (17%) was formed in the reaction.

According to the IR spectral data and the results of elementary analysis and in analogy with the synthesis of 1,3,5-triphenylbenzene [7] and 1,3,5-trihetarylbenzenes (hetaryl = 2-furyl and 2-coumaronyl) [8], this compound is the product of cyclic crotonic condensation of three molecules of 1-methyl-2-(5'-acetyl-2'-furyl)benzimidazole (VI). Its structure was confirmed by alternative synthesis from VI.

The acetylation of II in the 5' position of the thiophene ring proceeds with great difficulty, and VIII is obtained in only 22% yield. A side product is also formed in 9% yield, evidently by cyclocondensation of three VIII molecules.

The benzoylation of I and II with benzoic acid was also carried out by the Gardner method but at a higher temperature (150°C). The formation of 5'-benzoyl derivatives IX and X proceeds smoothly to give the products in high yields in this case.

We attempted to acylate I and II by means of o-substituted benzoic (with Cl, NO_2, NH_2, and OCH_3 substituents) and nicotinic acids. A positive result was obtained only with o-chlorobenzoic acid. 5'-(o-Chlorobenzoyl) derivatives XI and XII were synthesized in 47 and 72% yields.

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform or suspensions in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethylsiloxane as the internal standard.

1-Methyl-2-(5'-formyl-2'-hetaryl)benzimidazoles (III, V). A 10-mmole sample of I or II and 15-20 mmole of urotropin were heated at 70°C in 40 g of PPA, after which the reaction mixture was diluted with 150 ml of water, and the aqueous mixture was refluxed for 10 min and neutralized with sodium carbonate solution. The liberated reaction product was extracted with chloroform and chromatographed with a column packed with aluminum oxide by elution with chloroform.

1-Methyl-2-(5'-hydroxymethyl-2'-furyl)benzimidazole (IV). This compound was obtained in the synthesis of III and was identified by means of column chromatography. The yield of snow-white crystals, with mp 185-186°C (from alcohol), was 1.1 g (49%). IR spectrum: 1130 cm^{-1} (OH). Found: C 68.6; H 5.5; N 11.9%. $C_{13}H_{12}N_2O_2$. Calculated: C 68.4; H 5.3; N 12.3%.

1-Methyl-2-(5'-acetyl-2'-hetaryl)benzimidazoles (VI, VIII). A mixture of 10 mmole of I or II and 1.2 g (20 mmole) of glacial acetic acid in 40 g of PPA was stirred at 110°C, after which it was diluted with 150 ml of water, and the aqueous mixture was neutralized carefully with ammonium hydroxide. The reaction product was isolated just as in the preparation of III and V.

1,3,5-Tris[2'-(1-methyl-2-benzimidazolyl)-5'-furyl]benzene (VII). This compound was formed as a side product in the preparation of VI. The orange crystals had mp 233-234°C and were soluble in alcohol and chloroform. The yield of VII increased when the reaction temperature was raised to 140°C. According to the IR spectra data, the product did not contain a CO group. Found: C 76.1; H 4.4; N 12.8%. $C_{42}H_{30}N_6O_3$. Calculated: C 75.7; H 4.5; N 12.6%. The alternative synthesis of VII was carried out by heating VI in PPA at 140°C for 10 h; the product was obtained in 35% yield.

1-Methyl-2-(5'-benzoyl-2'-hetaryl)benzimidazoles (IX-XII). A 10-mmole sample of I or II and 20 mmole of benzoic or o-chlorobenzoic acid were stirred in 40 g of PPA at 150°C, after which the benzoylation product was isolated as in the case of III and V.

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