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REACTION OF 2-CHLOROMETHYLBENZIMIDAZOLES WITH ACETYLACETONE AND BENZOYLACETONE. BASIC BREAKDOWN OF β-DIKETONES

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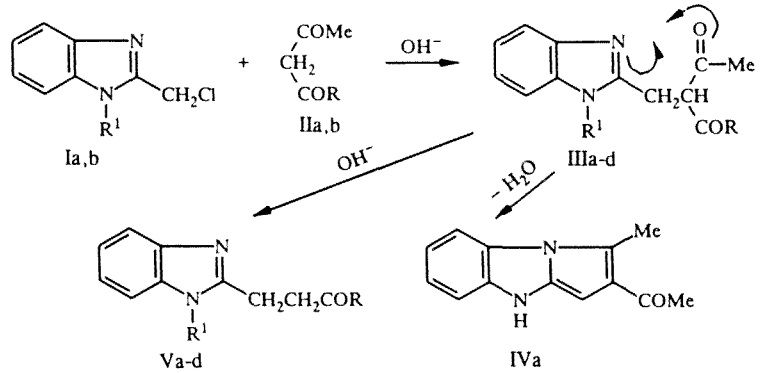
Base treatment of the products of alkylation of β-diketones by 2-chloromethylbenzimidazole under phase transfer catalysis (PTC) conditions causes loss of the acetyl group and formation of methylethyl- or ethylphenyl ketones.

Through an investigation of the reaction of 2-chloromethylbenzimidazole (Ia) with acetylacetone (IIa) under basic catalytic conditions it was found that the monoalkylation product (diketone IIIa) can form 1-methyl-2-acetylpyrrolo[1,2-a]benzimidazole (IVa) via an intramolecular condensation involving loss of water [1]. Subsequently, a detailed PMR and mass spectral study has shown that the reaction product contains not only the basic compound IVa but also a mixture of diketone IIIa and ketone Va; the latter being formed through a base catalyzed fission reaction of IIIa.



I a R^1 = H, b R^1 = Me; II a R = Me, b R = Ph; III, V a R = Me, R^1 = H, b R = R^1 = Me; c R = Ph, R^1 = H; d R = Ph, R^1 = Me

The mass spectrum of the reaction mixture shows signals for the cation radicals of IIIa, IVa, and Va with *m/z* 230 (16), 212 (7), and 188 (12). Fragmentations of the radicals with *m/z* 230 and 188 via separation of an acetyl radical or a hydrogen atom give an *m/z* 187 cation which is stabilized and can rearrange to a quinoxaline derivative with base ion *m/z* 187 (100). This cation is also apparently formed by fission of an ethyne radical from IVa with *m/z* 212 (Table 2).

The PMR spectrum of this mixture shows signals for IVa (see Table 1) together with a methine signal at 4.2 (1H, t) and methylene at 4.0 ppm (2H, d) for IIIa as well as two triplets at 3.45 and 3.4 ppm for the protons of Va. The signals of the $COCH_3$ groups in IIIa and Va overlap that of the acetyl in IVa and increase its integrated intensity. Calculation based on the difference in the values of the integrated intensities of the $COCH_3$ and CH_3 signals gave mass fractions for IIIa and Va of 8.5 and 9.5%.

Methylation of IVa by dimethylsulfate under PTC conditions (50% NaOH-acetone, TEBAC) at 20°C gives a difficultly separable mixture. The preparation of 1,4-dimethyl-2-acetylpyrrolo[1,2-a]-benzimidazole IVb was achieved by heating IVa with dimethylsulfate in DMF in the presence of potassium carbonate.

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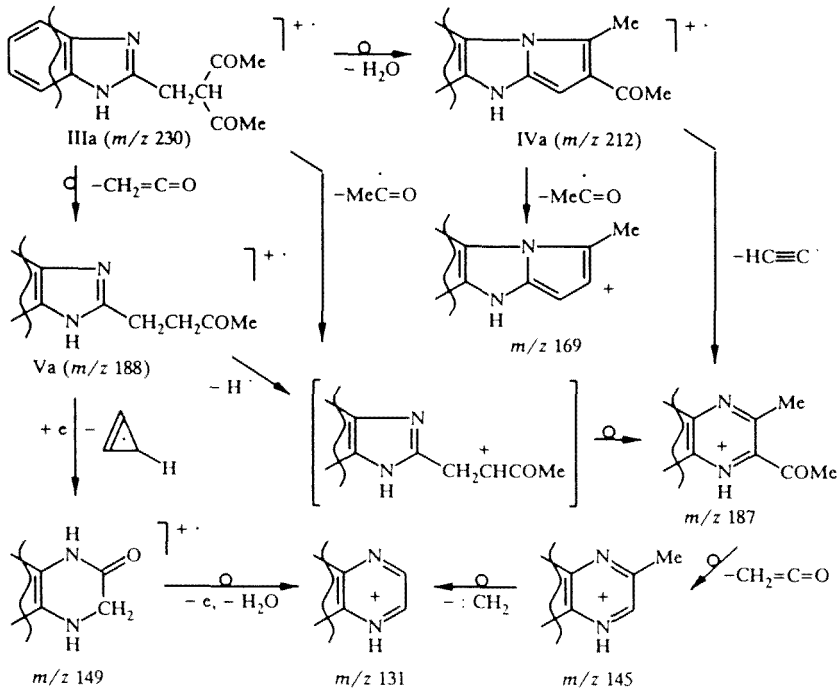
TABLE 1. Parameters for Compounds IVa, Vb-d, and VI

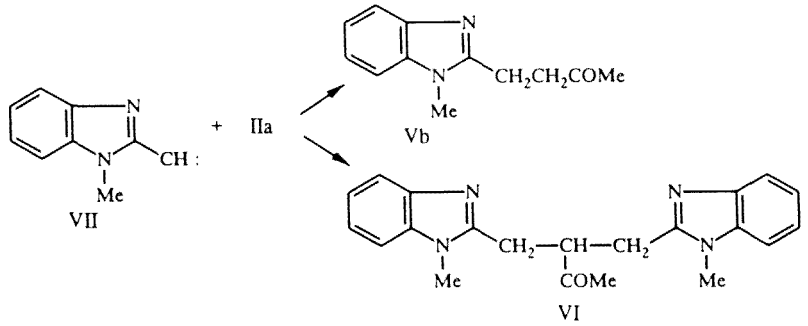
Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	PMR Spectrum, δ, ppm	Yield, %
		C	H	N			
IVa	$C_{13}H_{12}N_2O \cdot H_2O$	67.4 67,8	5.8 6,1	12.0 12,2	192...193	7,25 (5H,m, Ar), 2,1 (3H, s, $COCH_3$), 1,9 (3H, CH_3)	80
Vb†	$C_{12}H_{14}N_2O$	70.0 71,3	6.5 6,9	14.1 13,9	76	7,4 (1H,m, Ar), 7,0 (3H, m, Ar), 3,4 (3H, s, $N-CH_3$), 2,8 (4H,m, CH_2CH_2), 2,0 (3H, s. $COCH_3$)	35
Vc	$C_{16}H_{14}N_2O$	76.6 76,8	5.8 5,6	10.8 11,2	230	7,5 (2H,m, Ar), 7,1 (7H,m, Ar), 3,3 (4H, m, CH_2CH_2)	55
Vd	$C_{17}H_{16}N_2O$	76.9 77,3	6.0 6,1	10.5 10,6	110	7,5 (3H,m, Ar), 7,1 (6H,m, Ar), 3,3 (4H,m, CH_2CH_2), 3,7 (3H,s:, NCH_3)	50
VI	$C_{21}H_{22}N_4O$	72.5 72,8	6.6 6,4	15.8 16,2	164...165	7,2 (8H,m, Ar), 4,0...3,0 (5H,m, CH_2CHCH_2), 3,7 (3H, s, NCH_3)	43

*Solvent for crystallization: for IVa, VI) aqueous dioxane; Vb) hexane; Vc) DMF; Vd) aqueous alcohol.

†PMR Spectrum taken in CCl_4.



Reaction of 1-methyl-2-chloromethylbenzimidazole (Ib) with acetylacetone also occurs ambiguously. Treatment of Ib with base under PTC conditions yields 1-methyl-2-benzimidazolylcarbene (VII) which immediately reacts with a rather powerful nucleophile or is itself dimerized to give 1,8-dimethylpyrazino-[1,2-a:4,5-a']bisbenzimidazole (VIII) [1]. The reaction products of Ib with β-diketone IIa include a small amount of VIII together with the methylethyl ketone Vb and the 2-acetylpropane VI. Apparently reaction of the carbene VII with the acetylacetone anion gives mono- and dialkylation products of the latter (a substituted β-diketone) which undergoes fission in PTC conditions similarly to β-diketone IIIa. Mass and PMR spectra of V confirm their structure (Tables 1 and 2).



Formation of C-mono- and dialkylation derivatives has been noted in the reactions of acetylacetone with different alkylating reagents under PTC conditions [2]. However, in this case, examples of acidic fission of substituted β-diketones analogous to those observed in a number of benzimidazoles was not detected. The ease of fission of β-diketones in the 2-benzimidazole series is apparently due to the powerfully electrophilic effect of the 2-benzimidazole fragment [3].

In contrast to the acetylacetone reaction, that with benzoylacetone occurs unambiguously. In this case, the mono substituted β-diketone derivatives of IIb (compounds IIIc,d) evidently occur only as intermediates and are less stable than IIIa,b since traces of them are not observed in the reaction mixture. They are readily deacetylated in the presence of base to form the ethylphenyl ketones Vc,d. The latter are unstable under electron impact conditions. The mass spectra of Vc,d show weak signals for molecular ion peaks M^+ at *m/z* 250 (6) and 264 (9) respectively. The basic route for fragmentation of these ions is separation of a free benzoyl radical to form the base 2-ethyl- and 1-methyl-2-ethylbenzimidazole cations (with *m/z* 145 (100) and 159 (100)) which capture a hydrogen atom to form the 2-ethylbenzimidazole cation radicals with *m/z* 146 (11) and 160 (14).

TABLE 2. Mass Spectra of IVa, Vb-d, and VI*

Compound	m/z ($I_{rel.}$, %)
IVa	230 (16), 212 (7), 187 (100), 169 (10), 159 (6), 149 (51), 145 (29), 144 (9), 143 (9), 132 (5), 131 (8), 118 (5)
Vb	203 (15), 202 (15), 159 (100), 145 (11), 121 (5)
Vc	250 (6), 146 (11), 145 (100), 105 (9), 77 (15)
Vd	265 (9), 264 (9), 160 (14), 159 (100), 104 (11), 77 (23)
VI	347 (18), 346 (12), 303 (74), 303 (74), 202 (8), 201 (65), 171 (8), 170 (5), 157 (19), 156 (7), 147 (12), 146 (100), 145 (24), 130 (22), 77 (88)

*Ion peaks with intensity greater than 5% of the maximum value are given.

EXPERIMENTAL

IR Spectra were recorded on a UR-20 instrument for Vaseline oils and PMR spectra on a Tesla BS-487 instrument (80 MHz) with CF_3COOH solvent and HMDS internal standard. Mass spectra were obtained on a MAT-311 A spectrophotometer with direct introduction of the sample into the ion source, accelerating voltage of 3.0 kV, ionization energy 70 eV, cathode emission current 1.0 mA, and ionization chamber temperature 150°C.

Chromatography was carried out on Brockmann activity III Al_2O_3. Physicochemical and PMR parameters for the compounds obtained are given in Table 1 and mass spectral data in Table 2.

Elemental analytical data for C, H, and N agreed with that calculated.

1-Methyl-2-acetylpyrrolo[1,2-a]benzimidazole (IVa). TEBAC (0.1 g) and Ia (3 ml, 0.02 mole) were added with vigorous stirring to a mixture of sodium carbonate (2.2 g, 0.02 mole), water (5 ml), and dioxane (3 ml). After 15 min, acetylacetone (IIa, 3 ml, 0.02 mole) was added and the product was stirred for 3 h and stood overnight. It was then acidified with dilute HCl to pH 4, filtered, and the filtrate neutralized with ammonia. The precipitate was filtered off to give IVa (3.5 g). After three crystallizations from aqueous dioxane the product was shown by PMR spectroscopy to contain admixtures of IIIa (8.5%) and Va (9.5%). IR Spectrum: 1712 cm^{-1} (C=O).

1,4-Dimethyl-2-acetylpyrrolo[1,2-a]benzimidazole (IVb, $C_{14}H_{14}N_2O$). Compound IVa (2.1 g, 0.01 mole) was methylated by heating on a steam bath with dimethylsulfate (2 ml, 0.02 mole) and powdered potassium carbonate (2.8 g, 0.02 mole) until evolution of gas ceased. The product was diluted with water, extracted with ether, and chromatographed on Al_2O_3 and then silica gel. Benzimidazole IVb (0.7 g, 31%) was obtained as a light yellow oil, darkening in air. The melting point of the pictrate was 190°C (from alcohol).

4-(1-Methyl-2-benzylimidazolyl)-butan-2-one (Vb), and 1,3-di(1-methyl-2-benzimidazolyl)-2-acetylpropane (VI). Compound Ib (3.6 g, 0.02 mole) was added portionwise with vigorous stirring to a mixture of NaOH (50%, 5 ml), dioxane (5 ml), TEBAC (0.1 g), and acetylacetone (3 ml, 0.02 mole). The product was stirred for 5 h and diluted with water. The aqueous layer was poured off from the oily residue which was further treated with HCl (10%, 20 ml). The precipitated VIII hydrocloride was filtered (yield 0.1 g calculated on the free base), the mother liquor neutralized with ammonia, the aqueous layer poured off, and the residue triturated with iced water to yield a precipitate of Vb and VI which was filtered off and dried (3.2 g). Compound Vb was extracted with hexane and the hexane insoluble compound VI was chromatographed on an Al_2O_3 column (ether–chloroform, 2:1) and then crystallized from aqueous dioxane. The yields were 1.4 g (35%) for Vb and 1.5 g (43%) for VI. The IR spectra Vb and VI showed C=O bands at 1712 and 1720 cm^{-1} respectively.

2-(2-Benzimidazolyl)ethylphenyl ketone (Vc). Benzoylacetone (3.2 g, 0.02 mole) was added to a mixture of sodium carbonate (4.4 g, 0.04 mole), water (10 ml), TEBAC (0.1 g), acetone (10 ml), and DMSO (3 ml). The product was stirred for 10-15 min and Ia (3.3 g, 0.02 mole) was added. Stirring was continued for a further 6 h and the product was left overnight. With continued stirring, NaOH (40%, 3 ml) was added and then water (10 ml) after a further hour. The precipitate ws filtered, and washed with water and alcohol to give Vc (3.1 g). IR Spectrum: 1678 (C=O), 3000-3200 cm^{-1} (associated NH).

2-(1-Methyl-2-benzimidazolyl)ethylpheny6l ketone (Vd). Diketone IIb (3.2 g, 0.02 mole), TEBAC (0.1 g), acetone (10 ml), and DMSO (3 ml) were added to a solution of NaOH (1.2 g) and sodium carbonate (4 g) in water (10 ml) and then

Ib (3.6 g, 0.02 mole) was added with vigorous stirring. The product was stirred for 6 h, left overnight, acidified with HCl (5%), filtered, the filtrate neutralized with ammonia, and the precipitate filtered off to give Vd (2.9 g). IR Spectrum: 1675 cm^{-1} (C=O).

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