

RESEARCH ON UNSATURATED AZOLE DERIVATIVES

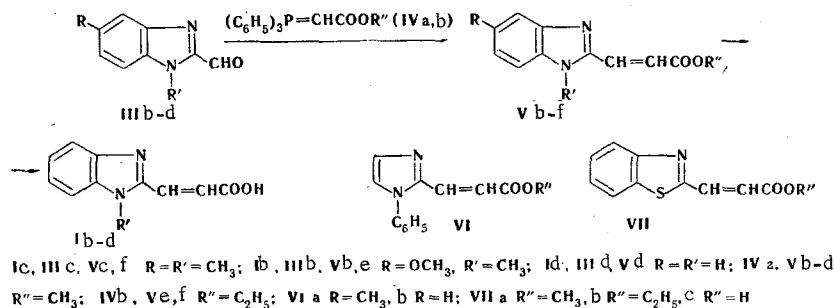
I. SYNTHESIS AND TRANSFORMATIONS OF α,β -UNSATURATED ACIDS IN THE AZOLE SERIES

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A number of esters of some β -(2-azolyl)acrylic acids were synthesized by means of the Wittig reaction and subjected to hydrolysis. The reaction of β -(1-methyl-2-benzimidazolyl)-acrylic acid and its derivatives with bromine was studied. It is shown that 1-methyl-2-ethynylbenzimidazole and 1,2-dimethylbenzimidazole are formed when methyl α -bromo- β -(1-methyl-2-benzimidazolyl)-acrylate is refluxed in sodium bicarbonate solution.

We have previously [1] described two methods for the synthesis of β -(1-methyl-2-benzimidazolyl)-acrylic acid (Ia) — by condensation of 1,2-dimethylbenzimidazole (IIa) with chloral and from 1-methyl-2-formylbenzimidazole (IIIa) by means of the Wittig reaction. Continuing these investigations, we have subjected 5-methoxy and 5-nitro derivatives of 2-methylbenzimidazole (IIb and c) to condensation with chloral. However, in contrast to IIa [1], IIb and IIc do not react with chloral. On the other hand, the reaction of formylbenzimidazoles with resonance-stabilized phosphoranes is apparently a general reaction [1, 2]. Thus the reaction of aldehydes IIb,c,d with carbalkoxymethylenetriphenylphosphoranes IVa,b proceeds quite smoothly on refluxing in benzene, and esters of β -(2-benzimidazolyl)acrylic acids (Vb,c,d) are formed in good yields (Table 1):



1-Phenyl-2-formylimidazole (IIIe) and 2-formylbenzothiazole (IIIg) react just as readily with phosphoranes IV; the yields of esters VIa and VIIa,b are quite high (Table 1).

Somewhat more severe conditions are necessary for the preparation of ester Vd: the reaction is carried out by prolonged refluxing of phosphorane IVa with aldehyde IIIc in dimethylformamide (DMF) — benzene (1:1); this is due to the polymeric structure of IIIc [3, 4].*

Esters V, VI, and VII are quite smoothly hydrolyzed when they are refluxed in alcoholic potassium hydroxide solution to give the corresponding β -azolylacrylic acids (I). The intense absorption band in the IR

* 2-Formylbenzimidazole is gradually depolymerized when it is refluxed in DMF and dimethyl sulfoxide (DMSO) [4].

TABLE 1. (2-Azoly)acrylic Acids and Their Esters

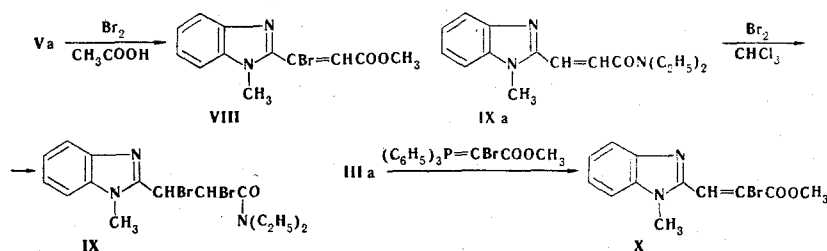
Com- pound	mp, °C	Crystallization solvent	Empirical formula	Found, %				Calc., %				Yield, %
				C	H	N	S	C	H	N	S	
Vd	180	Aqueous alcohol	C ₁₁ H ₁₀ N ₂ O ₂	65.3	4.9	13.5	—	65.2	5.0	13.9	—	70
Id	240 ^a	Alcohol	C ₁₀ H ₈ N ₂ O ₂	—	—	—	—	—	—	—	—	—
Vb	185—186	Toluene	C ₁₃ H ₁₄ N ₂ O ₃	63.8	6.0	11.6	—	63.4	5.7	11.4	—	68.0
Ve	132—133	Dioxane	C ₁₄ H ₁₆ N ₂ O ₃	64.9	6.1	10.9	—	64.6	6.2	10.8	—	62.0
lb	250	Alcohol	C ₁₂ H ₁₂ N ₂ O ₃	61.9	5.4	12.0	—	62.0	5.2	12.1	—	72.0
Vc	135—136	Aqueous alcohol	C ₁₃ H ₁₄ N ₂ O ₂	67.4	6.0	12.2	—	67.8	6.1	11.8	—	65.0
Vf	111—112	Aqueous alcohol	C ₁₄ H ₁₆ N ₂ O ₂	69.0	6.6	11.2	—	68.9	6.6	11.5	—	81.0
lc	240	Alcohol	C ₁₂ H ₁₂ N ₂ O ₂	66.5	5.5	12.9	—	66.7	5.8	12.6	—	75.0
Vla	115	Petroleum ether	C ₁₃ H ₁₂ N ₂ O ₂	68.8	5.3	12.4	—	68.4	5.3	12.3	—	93.0
Vlb	219 ^b	Water	C ₁₂ H ₁₀ N ₂ O ₂	—	—	—	—	—	—	—	—	87.0
Vlla	105	Aqueous alcohol	C ₁₁ H ₉ NO ₂ S	60.6	4.5	6.4	14.5	60.3	4.1	6.39	14.6	77
Vllb	89	Aqueous alcohol	C ₁₂ H ₁₁ NO ₂ S	61.4	4.9	6.2	13.3	61.8	4.8	6.0	13.7	78
Vllc	219 ^c	Alcohol	C ₁₀ H ₇ NO ₂ S	—	—	—	—	—	—	—	—	75

Note: ^aAccording to [13], mp 239°. ^bAccording to [14], mp 218—219°. ^cAccording to [15], mp 219°.

spectra of the acids and esters at 968–970 cm⁻¹ is evidence in favor of the predominant formation of the trans isomers of these compounds.

The reaction of acid Ia with bromine in chloroform or acetic acid leads to the formation of an extremely stable perbromide. Bromine adds to the C=C bond of acid Ia only upon the prolonged action of excess bromine in the light. This sort of phenomenon has been described for 4-styrylpyridine [5] and 5(6)-methyl-2-styrylbenzimidazole [6].

The methyl ester of acid Ia (Va) reacts with bromine in chloroform to give a perbromide; methyl β-(1-methyl-2-benzimidazolyl)-β-bromoacrylate (VIII) is formed in acetic acid with excess bromine.



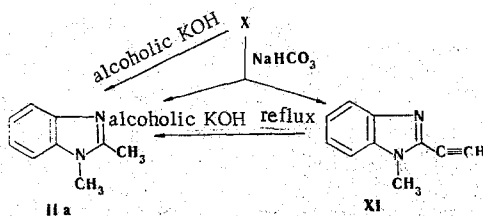
The reaction of the diethylamide of acid Ia with bromine proceeds somewhat more readily; it adds two atoms of bromine to give dibromo derivative IX.

The synthesis of methyl α-bromo-β-(1-methyl-2-benzimidazolyl)acrylate (X) can be realized by means of the Wittig reaction — by reaction of the previously described [7] carbomethoxybromomethylene-triphenylphosphorane (IVc) with aldehyde IIIa [11].

The coincidence of the absorption bands in the UV spectra of esters VIII and X (Fig. 1) is evidence in favor of the fact that the bromination of ester Va proceeds in the side chain. A hypsochromic shift of the maximum of the long-wave absorption as a consequence of disruption of conjugation in the carbonyl-group-heterocyclic-ring system (Fig. 2) is observed in the UV spectrum of diethylamide IX.

An attempt to realize the transition directly from β-(2-benzimidazolyl)acrylic acids to β-(2-benzimidazolyl)propionic acids by the usual method (bromination/dehydrobromination), as in the case of β-(2-benzothiazolyl)acrylic acid [8], was unsuccessful. Thus, for example, the action of a refluxing alcohol solution of potassium hydroxide on ester VIII gives resinous reaction products of polymeric structure (see [8]). Refluxing ester X in alcoholic potassium hydroxide solution gives 1,2-dimethylbenzimidazole (IIa), apparently as a consequence of cleavage of the products of dehydrobromination of ester X under the reaction conditions.* The use of a weaker base enabled us to change the direction of the reaction: The previously described [11] 1-methyl-2-ethynylbenzimidazole (XI) was isolated along with IIa when ester X was refluxed in sodium bicarbonate solution.

* See [9, 10] for this sort of cleavage of the C=C bond of 2-substituted benzimidazoles to give 2-methyl derivatives.



When XI is in turn refluxed in alcoholic potassium hydroxide solution, it is gradually converted to IIa.

These observations provide a basis for assuming that 1-methyl-2-ethynylbenzimidazole is an intermediate in the cleavage of the side chain of ester X to a methyl group.

EXPERIMENTAL

The UV spectra of methanol solutions of the compounds were recorded with an SF-4A spectrophotometer. The IR spectra of mineral oil pastes of acids VIII and of chloroform solutions of the esters were recorded with a UR-20 spectrometer.

General Method for the Preparation of β -(2-Azolyl)acrylic Acid Esters (V). A 0.01 mole sample of IVa or IVb and 0.01 mole of the appropriate aldehyde were refluxed in a solution of 20 ml of benzene for 8–12 h; the course of the reaction was monitored by means of TLC on aluminum oxide in chloroform. At the end of the reaction, the mixture was shaken with 40 ml of 5% hydrochloric acid. The hydrochloric acid extract was made alkaline with saturated sodium bicarbonate solution, and the precipitated ester was removed by filtration and washed with water. In the isolation of esters V, the solvent was first removed by distillation, and the reaction product was separated from the triphenylphosphine oxide by chromatography of the residue in ether on activity V aluminum oxide. The yields and melting points are presented in Table 1.

Ester Vd was obtained by refluxing a solution of 2-formylbenzimidazole with phosphorane IVa in a mixture of 3 ml of DMF and 3 ml of benzene for 40 h on an oil bath. The product was extracted with dilute hydrochloric acid.

Hydrolysis of β -(2-Azolyl)acrylic Esters. A 0.01 mole sample of the appropriate ester was refluxed for 4 h in 15% alcoholic potassium hydroxide solution. The alcohol was then removed by distillation, and the residue was dissolved in water. The unsaturated acid was isolated from the solution with dilute hydrochloric acid.

Methyl β -(1-Methyl-2-benzimidazolyl)- β -bromoacrylate (VIII). A 1.2 g (60 mmole) sample of ester Va [1] was dissolved in 5 ml of acetic acid, and 0.62 ml (12 mmole) of bromine in 3 ml of acetic acid was added dropwise with vigorous stirring. As the color of the bromine disappeared, a light-yellow precipitate (the perbromide) formed. The mixture was stirred for another 4 h, and the precipitate was removed by filtration, washed with acetic acid, shaken with sodium metabisulfate solution (to decompose the perbromide) and a saturated sodium bicarbonate solution, after which it was extracted with chloroform. The extract was dried with sodium sulfate, and the solvent was removed by distillation to give 1.1 g (73%) of colorless plates (from water) with mp 200–201° (dec.). The product was soluble in alcohol, benzene, and dioxane. The R_f value in CHCl_3 on a thin layer of activity V aluminum oxide was 0.8 (the R_f value of the starting ester was 0.6). The product decolorized a potassium permanganate solution, did not contain ionogenic halogen, and showed light-green fluorescence in UV light ($\text{C}=\text{C}$ conjugated with the ring). Found: C 48.8; H 4.2; Br 26.3; N 9.7%. $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_2$. Calculated: C 48.9; H 4.1; Br 26.8; N 9.6%. UV spectrum, λ_{max} , nm (log ϵ): 263 (3.57), 323 (4.37).

β -(1-Methyl-2-benzimidazolyl)- α,β -dibromopropionic Acid N,N-Diethylamide (IX). This compound was obtained in 76% yield as colorless needles (from aqueous alcohol) with mp 140° (dec.) by bromination of IXa [1] in chloroform, as in the case of ester VIII. The product did not decolorize aqueous potassium permanganate solution, did not contain ionogenic halogen, and did not fluoresce in UV light. Found: C 43.4; H 4.9; Br 38.1; N 10.3%. $\text{C}_{15}\text{H}_{19}\text{Br}_2\text{N}_3\text{O}$. Calculated: C 43.2; H 4.6; Br 38.3; N 10.1%. UV spectrum, λ_{max} , nm (log ϵ): 262 (4.04), 290 (4.2).

Methyl α -Bromo- β -(1-methyl-2-benzimidazolyl)acrylate (X). A 2.1 g (5 mmole) samples of bromophosphorane IVc was dissolved in 15 ml of benzene, 0.8 g (5 mmole) of IIIa was added, and the mixture was stirred to dissolve the solid completely. The mixture began to heat up, and light-yellow crystals of ester

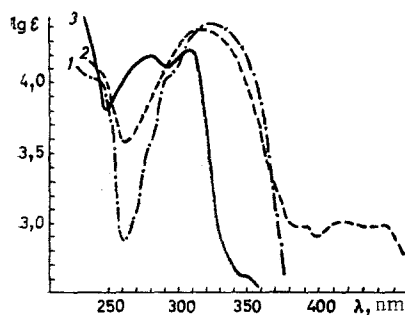


Fig. 1. UV spectra (in methanol): 1) Va; 2) VIII; 3) X.

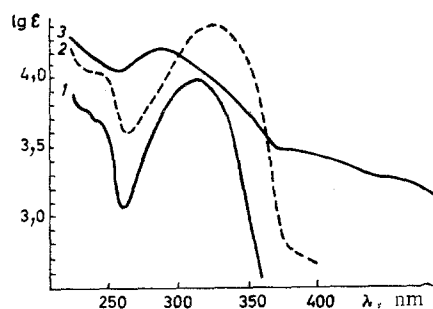


Fig. 2. UV spectra (in methanol): 1) Ia; 2) IXa; 3) IX.

X began to precipitate immediately. The mixture was heated on a water bath to dissolve the precipitate, and the mixture was allowed to stand in warm water for a brief time. It was then cooled, and the precipitated crystals of the ester were removed by filtration. Prolonged heating often led to resinification of the reaction products. The yield was 1.1 g (68%). The yellow prisms with a pale-green tint had mp 186° (dec., benzene) and were readily soluble in chloroform and dioxane and only slightly soluble in alcohol [11].

Reaction of Ester X with Sodium Bicarbonate. A 0.6 g (20 mmole) sample of X was refluxed in a solution of 1.4 g of sodium bicarbonate in 20 ml of water for 9 h, after which the dark oil (a mixture of IIa and XI) was extracted with chloroform and chromatographed on aluminum oxide. The solvent was removed by distillation, and the mixture of IIa and XI was separated on aluminum oxide in ether with collection of XI in the first portions of the eluate. The yield of XI with mp 100° (petroleum ether) (mp 100° [11]) was 0.075 g (24%). The yield of IIa with mp 112° [12] was 0.10 g (42%).

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