

RESEARCH ON UNSATURATED AZOLE DERIVATIVES

II.* SYNTHESIS AND TRANSFORMATIONS OF SOME

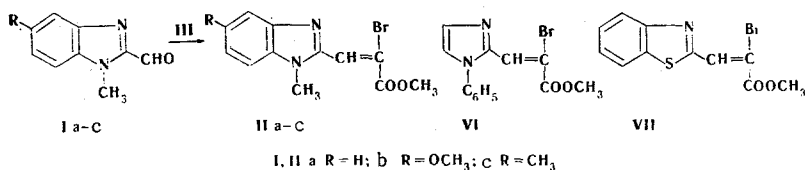
β -(2-AZOLYL)PROPIOLIC ACIDS

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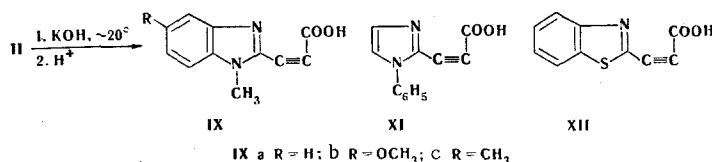
α -Bromo- β -(2-azolyl)acrylic acid esters, the dehydrobromination of which with alcoholic alkali gives β -(2-azolyl)propionic acids, were synthesized by means of the Wittig reaction. Some 2-ethynylbenzimidazoles were synthesized by thermal decarboxylation of the β -(2-benzimidazolyl)propionic acids. It is assumed that the ease of decarboxylation of these acids is due to the possibility of the formation by them of dipolar ions.

We have previously [1] described the synthesis of α -bromo- β -(1-methyl-2-benzimidazolyl)acrylic acid (IIa) by reaction of 1-methyl-2-formylbenzimidazole (Ia) with carbomethoxybromomethylenetriphenylphosphorane (III) [2]. Continuing these investigations in the azole series, we have introduced 5-substituted 2-formylbenzimidazoles (Ib,c) into the reaction with phosphorane III.



The reaction usually commences when solutions of I and III in benzene are mixed and proceeds with gentle warming of the reaction mixture. Esters of β -substituted α -bromoacrylic acids (IIa-c) are obtained in good yields. 1-Phenyl-2-formylimidazole (IV) [3] and 2-formylbenzothiazole (V) also react readily with phosphorane III to give esters VI and VII, respectively.

The only product in the reaction of ester IIa with a solution of potassium hydroxide at room temperature is the potassium salt of β -(1-methyl-2-benzimidazolyl)propionic acid, acidification of which gives acid IXa in high yield.



This reaction also proceeds just as readily with a number of other α -bromo-2-azolyl- β -acrylic acid esters (IIb,c, VI, and VII) to give the corresponding 2-azolylpropionic acids (IXb,c, XI, and XII).

* See [1] for communication I.

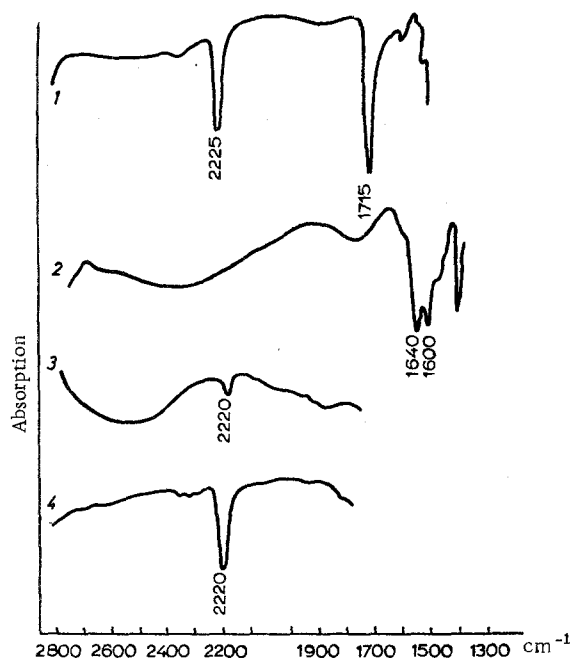


Fig. 1. IR spectra: 1) acid XI; 2) acid IXa; 3) potassium salt of IXa; 4) potassium salt of IXb.

TABLE 1. Absorption of the CO Group of β -(2-Azoly)propionic Acids and Their Hydrochlorides

| Compound | $\nu_{\text{CO}}, \text{cm}^{-1}$ | |
|----------|-----------------------------------|---------------|
| | acid | hydrochloride |
| IXa | 1600 | 1718 |
| IXb | 1628, 1643 | 1705 |
| IXc | 1700, 1720 | 1725 |
| XII | 1710 | 1712 |

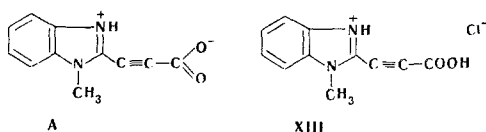
The ease of dehydrobromination of esters IIa-c, VI, and VII is apparently explained by the lability of both the halogen atom in the α -position relative to the carboxyl group and the hydrogen atom attached to the carbon atom bonded directly to the heterocycle ring.

Propiolic acids IXa,b and XI are stable for several hours only as the hydrates. They undergo spontaneous decarboxylation on air drying or over phosphorus pentoxide. However, the yields of the 2-ethynyl derivatives in this case and when the propiolic acids are heated in water are low ($\sim 20\%$). Decarboxylation of acids IXa-c and XI in vacuo makes it possible to raise the yields to 36-40% [3]. This process takes place more smoothly when alcohol suspensions of the compounds are refluxed. Acids IXa and XI are most readily decarboxylated in this case, acid IXb is decarboxylated with greater difficulty, and IXc is decarboxylated only on prolonged refluxing.

The ease of decarboxylation of acids IX is apparently due to weakening of the bond between the carboxyl group and the α -carbon atom of the acids under the influence of the concerted $-I$ effect of the $\text{C}=\text{C}$ group [4] and the 2-benzimidazolyl grouping [5]. The higher the thermal stability of acids IXa-c, the higher the ν_{CO} wave numbers in their IR spectra (Table 1).

Inasmuch as the resistance of acids IXa-c to decarboxylation is determined by the magnitude of the $-I$ effect of the benzimidazole ring, electron-donor substituents in the 5 position, by supplying electrons into the ring of the heterocycle, promote a decrease in this effect and an increase in the stability of the acids.

Considering the high dissociation constants of propiolic acids [6] and the quite high basicities of benzimidazole derivatives [7], one might assume that acids IXa-c, like 2-imidazolylcarboxylic acids [8], are decarboxylated through the intermediately formed unstable dipolar ion A.



The betaine structure of acids IXa-c is apparently the reason for masking of the absorption of the $\text{C}=\text{C}$ group in the IR spectra of these acids. In fact, the absorption bands of the betaine structure vanish in the spectra of their potassium salts, and the $\text{C}=\text{C}$ bond shows up usually quite distinctly at 2200 cm^{-1} (Fig. 1). The disappearance of the betaine structure when acids IXa-c are converted to the hydrochlorides has a substantial effect on the stabilities of the compounds: hydrochlorides XIII can exist for a long time without undergoing change. An increase in the frequencies of the stretching vibrations of the carboxyl group is observed in the IR spectra of the hydrochlorides of acids IXa-c (Table 1).

2-Benzothiazolylpropionic acid (XII) is crystallized from alcohol and does not undergo changes on prolonged refluxing. As a consequence of the low basicity of benzothiazole, the formation of a zwitterion is apparently hindered; this is responsible for the resistance of this acid to decarboxylation, just as in the case of thiazole-2-carboxylic acids [8]. The absence of betainization of this acid is confirmed by the IR spectral data: there is almost no shift in ν_{CO} on passing from the acid to its hydrochloride (Table 1).

The decarboxylation of acid XII at its melting point gives a dark viscous product of polymeric structure; this is probably associated with the low thermal stability of the 2-ethynylbenzothiazole that is formed in the process (see [9]).

TABLE 2. α -Bromo- β -(2-azolyl)acrylic Acid Esters

| Com-pound | mp, °C | Solvent | Empirical formula | Found, % | | | | Calc., % | | | | Yield, % |
|-----------|--------|---------------|------------------------|----------|-----|------|-----|----------|-----|------|-----|----------|
| | | | | C | H | Br | N | C | H | Br | N | |
| IIb | 186 | Ethyl acetate | $C_{13}H_{13}BrN_2O_3$ | 48.3 | 4.4 | 24.8 | 8.9 | 48.0 | 4.0 | 24.6 | 8.6 | 66.7 |
| IIc | 175 | Alcohol | $C_{13}H_{13}BrN_2O_2$ | 50.2 | 4.5 | 25.5 | 8.7 | 50.5 | 4.2 | 25.8 | 9.1 | 70 |
| VII | 76 | Alcohol | $C_{11}H_8BrNO_2S^*$ | 46.9 | 3.0 | 28.1 | 4.9 | 46.8 | 2.9 | 28.3 | 5.0 | 75 |

* Found: S 11.0%. Calculated: S 11.3%.

TABLE 3. β -(2-Azolyl)propionic Acids

| Com-pound | mp, °C | Solvent | Empirical formula | Found, % | | | Calc., % | | | IR spec-tra, cm ⁻¹ C \equiv C* | Yield, % |
|-----------|--------|---------|--------------------------|----------|-----|------|----------|-----|------|--|----------|
| | | | | C | H | N | C | H | N | | |
| IXb | 142 | — | $C_{12}H_{10}N_2O_3$ | 62.2 | 4.3 | 12.0 | 62.6 | 4.4 | 12.2 | 2290 | 85 |
| IXc | 218 | Alcohol | $C_{12}H_{10}N_2O_2$ | 67.0 | 4.4 | 12.8 | 67.3 | 4.7 | 13.1 | 2200 | 80 |
| XII | 203 | Dioxane | $C_{10}H_8NO_2S^\dagger$ | 59.2 | 2.8 | 7.2 | 59.1 | 2.5 | 6.9 | — | 76 |

* The IR spectrum of the potassium salt in mineral oil.

† Found: S 15.5%. Calculated: S 15.8%.

EXPERIMENTAL

The IR spectra of chloroform solutions or mineral oil pastes of the compounds were recorded with a UR-20 spectrometer.

Reaction of 2-Formylazoles with Carbomethoxybromomethylenetriphenylphosphorane (III). A 0.01 mole sample of the appropriate aldehyde I was added to a solution of 0.01 mole of III in 15-20 ml of benzene, and the mixture was stirred until all of the solid had dissolved. The mixture heated up appreciably, and yellowish crystals of II began to form immediately. To complete the reaction, the mixture was allowed to stand on a water bath at 40-60° for a certain time, after which it was heated to the boiling point and cooled. The crystals of esters II were removed by filtration and washed with benzene. Highly pure reaction products were obtained. This reaction proceeds so smoothly that it can be used for the qualitative determination of 2-formylbenzimidazoles.

No precipitate formed in the reaction of aldehydes IV and V with phosphorane III, and ester VI was therefore extracted at the end of the reaction with dilute hydrochloric acid and treated with sodium bicarbonate. In order to isolate ester VII, the solvent was removed by distillation, and the reaction product was chromatographed with a column filled with aluminum oxide in ether to separate the triphenylphosphine oxide; the first portions of the eluate were collected.

β -(2-Azolyl)propionic Acids. A 0.01 mole sample of II was mixed with a solution of 4 g of potassium hydroxide in 30 ml of alcohol, and the mixture was allowed to stand overnight at room temperature. It was then filtered to remove the precipitate, which was a mixture of the potassium salt of the acid (only slightly soluble in alcohol) and potassium bromide. The precipitate was washed with alcohol and dissolved in water, and the solution was acidified with dilute hydrochloric acid. The precipitated acid was removed by filtration and dried at 60°. The melting points and the yields are presented in Table 3.

Acids XI and XII were obtained in the same way as acids IXa-c, but, inasmuch as their potassium salts are quite soluble in alcohol, the reaction mixture was filtered to remove the potassium bromide, the solvent was evaporated without heating, and the residue was dissolved in water. The aqueous solution was then acidified with hydrochloric acid.

Acids IIa-c and XI gradually decarboxylated on storage. Their hydrates (in water), hydrochlorides (in HCl solution), or salts (in alkaline solution) are more stable. They were purified by reprecipitation from aqueous alkali solutions. Compound IXc can be recrystallized from alcohol by careful heating. Compound XII can also be obtained by treatment of VII with boiling alcoholic potassium hydroxide solution (see [2]) and, after isolation, can be recrystallized from alcohol or dioxane.

1-Methyl-2-ethynyl-5-methoxybenzimidazole (Xb). A 2.3 g (0.01 mole) sample of IXb was heated in 20 ml of alcohol on a water bath until the solid had dissolved completely and vigorous carbon dioxide evolution had ceased. The alcohol solution was evaporated without heating in a stream of air, and the residue

was chromatographed on aluminum oxide, in chloroform. The solvent was evaporated to give 1.65 g (89%) of shiny pale-rose plates with mp 162-163° (ethyl acetate), which were quite soluble in benzene, alcohol, and chloroform. Found: C 70.6; H 5.5; N 15.2%. $C_{11}H_{10}N_2O$. Calculated: C 70.9; H 5.4; N 15.0%. IR spectrum ($CHCl_3$): 3310 cm^{-1} ($C\equiv CH$).

1,5-Dimethyl-2-ethynylbenzimidazole (Xc). This compound was obtained by prolonged refluxing of acid IXc in alcohol. It was isolated (in 52% yield) in the same way as Xb. The light-yellow shiny plates had mp 138° (from alcohol-ether). Found: C 77.5; H 6.2; N 16.8%. $C_{11}H_{10}N_2$. Calculated: C 77.6; H 6.3; N 16.5%. The IR spectrum ($CHCl_3$) contained an intense absorption band at 3310 cm^{-1} ($C\equiv C-H$).

LITERATURE CITED

1. I. I. Popov, A. M. Simonov, V. I. Mikhailov, and N. A. Sil'vanovich, *Khim. Geterotsikl. Soedin.*, 408 (1974).
2. G. Märkl, *Chem. Ber.*, 94, 2996 (1961).
3. A. M. Simonov and I. I. Popov, *Khim. Geterotsikl. Soedin.*, 140 (1971).
4. G. Mansfield and M. C. Witting, *J. Chem. Soc.*, 4781 (1956).
5. H. Walba, W. I. Murray, G. Knitson, and A. Diaz, *J. Am. Chem. Soc.*, 88, 1962 (1966).
6. R. A. Raphael, *Acetylenic Compounds in Organic Synthesis*, London (1955).
7. *Outline of the Chemistry of Azoles* [in Russian], Izd. Rostovsk. Univ., Rostov-on-Don (1965).
8. P. Haake, L. P. Bausher, and J. P. McNeal, *J. Am. Chem. Soc.*, 93, 7045 (1971).
9. I. I. Popov and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 122 (1971).