Investigation on Some (*E*)- and (*Z*)-3-Heterocyclic-substituted-2-phenylacrylic Acids

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The synthesis of 3-(2-thiazolyl)-, 3-(2-benzothiazolyl)- and 3-(2-benzo[*b*]thienyl)-2-phenylacrylic acids is reported. Spectroscopic analyses and p*Ka* determinations were found to be a convenient method for distinguishing the *E* and *Z* geometrical configurations.

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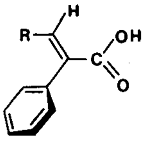
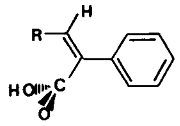
Interesting studies have been reported on 3-heterocyclicsubstituted-2-phenylacrylic acids (1-4). We thought it would be useful to investigate the 3-(2-thiazolyl)- (Ia,b), 3-(2-benzothiazolyl)- (IIa,b) and 3-(2-benzo[*b*]-thienyl)-(IIIa,b) analogues.



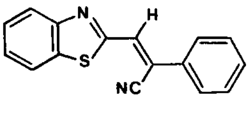
(*E*)-(I,II,III)a



(Z)-(I,II,III)b

I : R = 2-thiazolyl
II : R = 2-benzothiazolyl
III : R = 2-benzo[b]thienyl

These compounds were obtained by Perkin condensation of phenylacetic acid with the appropriate aldehydes prepared by known methods. The reaction with 2-thiazolecarbaldehyde performed at 105° for 0.5 hour gave the single *E* isomer Ia, while at 10° for 3 hours it gave a mixture of *Z/E* isomers in a ratio 3/2, as determined by quantitative tlc. At higher temperature the reaction occurs with better yields, but we found that the *Z* acid, under the same conditions, was completely converted into the *E* isomer. The same condensation starting from 2-benzothiazolecarbaldehyde, performed at 50° well as at 10° gave only *E* acid IIa. We therefore prepared the *Z* isomer IIb by hydrolysis of 2-phenyl-3-(2-benzothiazolyl)acrylonitrile (IV):

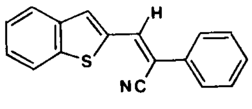


IV

Evidence for the *Z* structure of IV was provided by its uv spectrum. This has the longest wavelength band at 354 nm, with very high molar extinction coefficient, due to the extended conjugation of the *p*-electron system of the heterocyclic ring with the styryl side chain. The *Z* acid IIb so obtained, under the same conditions that led to the tormation of the single *E* isomer IIa, at 50° isomerizes while at 10° it remains unaltered. Therefore the conformation of the addition intermediate, before water elimination, could account for the presence of only the *E* isomer IIa at the lower temperature.

The reaction between 2-benzo[*b*]thiophenecarbaldehyde and phenylacetic acid always led to the *E* isomer IIIa, both when operating at 105° for 0.5 hour or at 10° for 3 hours. We tried to perform the condensation in ethanol and potassium hydroxide at 20°, but after 24 hours we again obtained the *E* isomer IIIa in very good yields.

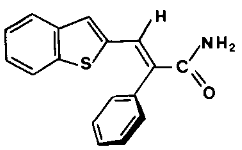
Just as for the benzothiazolyl derivative, we decided to prepare the *Z* isomer IIIb by hydrolyzing 2-phenyl-3-(2-benzo[*b*]thienyl)acrylonitrile (V) (5), whose *Z* configuration was determined by its uv spectrum.



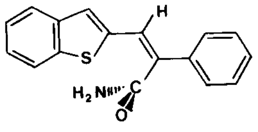
V

The hydrolysis was carried out in alkaline medium. After acidification, together with another product that was found to be 2-benzo[*b*]thiophenecarboxylic acid, only the *E* isomer IIIa was obtained. The hydrolysis, when carried out in concentrated hydrochloric acid for 2 hours, also led to the same single *E* isomer.

To avoid an eventual isomerization of the final *Z* acid, the reaction time was reduced. After 1 hour, besides the unaltered *Z* nitrile V, only small quantitites of the two 2-phenyl-3-(2-benzo[*b*]thienyl)acrylamides (VIa and VIb) were isolated.



VIa



VIb

The formation of compound VIa suggests clearly that the isomerization occurs already at the acrylamide stage. To confirm the *E* structure, compound VIa was also syn-

Table 1

Spectral Data and p*K*a Values

Compound	Isomer	IR ν max cm^{-1} (a)	NMR δ, ppm (b)	UV, λ max (Log ε) (c)	p*K*a
Ia	*E*	1695 (C=O), 1630 (C=C)	8.10 (s, 1H, ethylenic)	238 (3.81), 245 sh (3.78), 283 sh (3.91), 308 (4.08)	6.00
Ib	*Z*	1705 (C=O), 1615 (C=C)	7.30 (s, 1H, ethylenic)	228 (3.98), 316 (4.38)	4.78
IIa	*E*	1695 (C=O), 1622 (C=C)	8.15 (s, 1H, ethylenic)	207 (4.51), 225 (4.40), 247 sh (3.83), 255 sh (3.77), 315 (4.27)	5.72
IIb	*Z*	1705 (C=O), 1615 (C=C)	7.38 (s, 1H, ethylenic)	213 (4.39), 262 (3.84), 329 (4.48)	4.61
IIIa	*E*	1680 (C=O), 1610 (C=C)	8.18 (s, 1H, ethylenic)	215 (4.38), 234 (4.27), 258 (3.91), 265 sh (3.85), 323 (4.48)	6.46

(a) Potassium bromide. (b) Solvent: acetone-d_6. (c) Solvent: methanol.

thesized from acid IIIa. The spectral data, together with the p*K*a values of the obtained acrylic acids, are reported in Table 1.

Owing to the greater conjugation of the *Z* isomers, due to the coplanarity of the heterocycle with the phenyl ring, we found the expected red-shift and absorptivity increase of the longest wavelength uv bands of Ib, IIb with respect to Ia, IIa. Since, on the other hand, the phenyl ring in the *E* isomers is out of the plane of the main conjugation involving the carboxyl group, the *E* configuration of 2-phenyl-3-(2-benzo[*b*]thienyl)acrylic acid (IIIa) was confirmed by comparison of its spectrum with that of methyl 3-(2-benzo[*b*]thienyl)acrylate (6).

Unequivocal evidence for the stereochemical structures of our synthesized acids was provided by the chemical shift of the ethylenic proton singlet. In the compounds with *E* structure, in fact, such a signal, for the deshielding effect of the conjugated carboxyl group, appears between δ 8.10-8.18, while in the *Z* isomers the same is shifted upfield to δ 7.30-7.38. Moreover, as expected, the ir stretching frequencies of the carbonyl group appear at 1705 and 1695 cm^{-1} for the *Z* and *E* isomers respectively. On the other hand, a shift in the opposite direction was found for the ν C=C (2).

The p*K*a values emphasize the higher acidity of the *Z* isomers due to the deconjugation of the carboxyl group (7).

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 283 spectrophotometer; ^{1}H-nmr spectra were obtained on a Perkin-Elmer R 32 instrument; chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. The uv spectra were recorded on a Cary 14 spectrophotometer. The p*K*a values were obtained with the usual potentiometric procedure (8) at 25 ± 0.1° from 3.7×10^{-3} *M* solutions in 2-methoxyethanol/water 80/20. Melting points are uncorrected.

(*E*)- and (*Z*)-2-Phenyl-3-(2-thiazolyl)acrylic Acids (Ia,b).

Into a stirred solution of 6.8 g (50 mmoles) of phenylacetic acid and 5.6 g (50 mmoles) of 2-thiazolecarbaldehyde in 15 ml of acetic anhydride, 7 ml of triethylamine were slowly added. The solution was refluxed for 0.5 hour, cooled, then acidified with dilute sulfuric acid and extracted with ether; the organic layer was washed several times with 5% sodium hydroxide, then the alkaline solution was carefully acidified until the *p*H was 5. The resulting *E* isomer Ia was filtered and recrystallized from ethanol (8.3 g, 75%), mp 196-197°. The filtrate, brought to *p*H 1, gave an addition crop (1.2 g, 10%) of the same isomer.

Anal. Calcd. for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.05. Found: C, 62.15; H, 3.96; N, 6.24.

The same reaction performed at 10° for 3 hours yielded both isomers. Compound Ia (2.4 g, 21%) was collected at pH5. By acidifying the filtrate to pH1, Ib was separated out and recrystallized from ethanol (3.7 g, 32%), mp 182-183°.

Anal. Calcd. for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.05. Found: C, 62.28; H, 3.86; N, 6.00.

From the reaction at 10°, by complete precipitation at *p*H 1, it was possible to determine the *E/Z* ratio of the resulting isomers by the tlc on silica gel F_{254} plates, using benzene/ethanol/acetic acid (10/5/1) as mobile phase. The spots with Rf 0.83 and 0.75, that were found to correspond to *E* and *Z* isomers respectively, were extracted with methanol and then determined by uv spectroscopy.

(*E*)-2-Phenyl-3-(2-benzothiazolyl)acrylic Acid (IIa).

The reaction was carried out as described for Ia starting from 2-benzothiazolecarbaldehyde maintaining the temperature between 5° and 10° for 3 hours. From the solution, acidified to *p*H 5, the solid product was collected and recrystallized from ethanol (9.6 g, 68%), mp 226-227°. From the filtrate, by precipitation at *p*H 1, an additional crop of the same compound (1.8 g, 13%) was obtained.

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.31; H, 3.93; N, 4.97. Found: C, 68.50; H, 4.14; N, 5.14.

(*Z*)-2-Phenyl-3-(2-benzothiazolyl)acrylonitrile (IV).

Into a stirred solution of 3.0 g (18 mmoles) of 2-benzothiazolecarbaldehyde and 2.1 g (18 mmoles) of phenylacetonitrile in 20 ml of ethanol, 1 ml of 30% potassium hydroxide was added. The solution was heated at 50° for 1 hour; during the course of the reaction a yellow powder appeared. After cooling, the solid product was filtered and recrystallized from ethanol (4.3 g, 91%), mp 119-120°; ir (potassium bromide): 2215 cm^{-1} (C≡N); nmr (DMSO-d_6): 8.36 (s, 1H, ethylenic); uv (methanol): 227 sh (4.21), 225 sh (3.73), 280 sh (3.73), 354 (4.48).

Anal. Calcd. for $C_{16}H_{10}N_2S$: C, 73.25; H, 3.84; N, 10.68. Found: C, 73.46; H, 3.75; N, 10.43.

(*Z*)-2-Phenyl-3-(2-benzothiazolyl)acrylic Acid (IIb).

A suspension of the nitrile IV (4.0 g) in 75 ml of concentrated hydrochloric acid was refluxed. After a few minutes, a solution was formed from which immediately a solid product precipitated. After cooling, the solid was filtered and recrystallized from ethanol (4.0 g, 94%), mp

213-214°.

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.31; H, 3.93; N, 4.97. Found: C, 68.45; H, 4.16; N, 5.20.

(*E*)-2-Phenyl-3-(2-benzo[*b*]thienyl)acrylic Acid (IIIa).

The reaction was carried out at described for Ia starting from 2-benzo[*b*]thiophenecarbaldehyde. From the solution, acidified until the *p*H was 5, the resulting solid was filtered and recrystallized from ethanol (9.8 g, 70%), mp 235-236°. The filtrate was brought to *p*H 1 and an additional crop of the same compound was obtained (1.6 g, 12%).

Anal. Calcd. for $C_{17}H_{12}O_2S$: C, 72.82; H, 4.31. Found: C, 72.87; H, 4.32.

(*Z*)-2-Phenyl-3-(2-benzo[*b*]thienyl)acrylonitrile (V).

This compound was synthesized according to the procedure of Shirley (5); ir (potassium bromide): 2210 cm^{-1} (C≡N); nmr (DMSO-d_6): 8.39 (s, 1H, ethylenic); uv (methanol): 217 (4.39), 237 (4.13), 274 (3.71), 354 (4.57).

(*E*)- and (*Z*)-2-Phenyl-3-(2-benzo[*b*]thienyl)acrylamides (VIa,b).

A suspension of V (4.0 g) in 75 ml of concentrated hydrochloric acid was refluxed for 1 hour, then the hot reaction mixture was filtered. The solid (3.8 g) was identified as unreacted starting nitrile. From the solution, after cooling, a crude product separated. From tlc evidence (silica gel F_{254} plates, chloroform as eluent) it was found to be a mixture of two compounds with Rf 0.66 and 0.33.

The compound with lower Rf was identified as (*E*)-2-phenyl-3-(2-benzo[*b*]thienyl)acrylamide (VIa), mp 209-210°; ir (potassium bromide): 1450, 1350 cm^{-1} (NH_2), 1650 cm^{-1} (C=O); nmr (DMSO-d_6): 7.92 (s, 1H, ethylenic); uv (methanol): 215 (4.45), 234 (4.29), 258 (3.90), 267 sh (3.84), 321 (4.49).

Anal. Calcd. for $C_{17}H_{13}NOS$: C, 69.13; H, 4.43; N, 4.74. Found: C, 69.35; H, 4.57; N, 4.63.

The compound with higher Rf was identified as (*Z*)-2-phenyl-3-(2-benzo[*b*]thienyl)acrylamide (VIb), mp 194-195°; ir (potassium bromide): 1380, 1200 cm^{-1} (NH_2), 1640 cm^{-1} (C=O); nmr (DMSO-d_6): 7.32 (s, 1H, ethylenic; uv (methanol): 218 (4.34), 232 sh (4.15), 265 sh (3.88), 273 (3.91), 325 sh (4.51), 330 (4.52), 345 sh (4.35).

Anal. Calcd. for $C_{17}H_{13}NOS$: C, 69.13; H, 4.43; N, 4.74. Found: C, 69.27; H, 4.32; N, 4.57.

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