The supernatant was saturated with CO_2 to remove excess $Ba(OH)_2$ and centrifuged. After removal of excess $Ba(OH)_2$, the aqueous solution was concentrated *in vacuo* on a water bath. The dried residue was triturated with acetone to give a white powder, this powder was dissolved in water, and precipitated again with acetone. The sample for analysis was dried over P_2O_5 *in vacuo* at 100—110° to constant weight. *Anal.* Calcd. for $(C_4H_6O_3N_2P)_2Ba$: C, 20.84; H, 3.07; N, 12.15. Found: C, 20.97; H, 3.09; N, 12.63. IR ν_{max}^{KBr} cm^{-1}: 1170, and 1140 (phosphoryl groups). NMR (in D_2O) τ: 6.65 (3H, s, $\text{N-C}\underline{\text{H}}_3$), 2.85 (2H, m, $\text{C}\underline{\text{H}}\text{=C}\underline{\text{H}}$) and 2.25 (1H, m, $\text{N-C}\underline{\text{H}}\text{=N}$).

Benzyl (4i) and Bornyl (4j) Dihydrogen Phosphate——A solution of 0.82 g (0.01 mole) of H_3PO_3, 3.00 g (0.01 mole) of $HgCl_2$, and 3.28 g (0.04 mole) of N-methylimidazole in dry acetonitrile (2 ml) was warmed rapidly to 80°. After additional stirring for 1 hr, 1.40 g (0.013 mole) of benzyl alcohol was added. Stirring was continued at 80° for 4 hr. Precipitated metallic Hg was filtered off, the filtrate was evaporated under a reduced pressure, and the oil was desalted through a column (12 × 200 mm) of Amberlite IR-120 resin (H^+ form) prepared in 50% EtOH, followed by elution with the same solvent. The collected eluate (between 40 and 120 ml fractions) was concentrated, the oily residue was dissolved in 5 ml of 95% EtOH, and then 1.5 ml of aniline was added to the solution. The mixture was kept standing in a refrigerator overnight. A white precipitate separated and was collected by filtration. Dianilinium salt of benzyl dihydrogen phosphate (**4i**) (2.97 g, 81%) was obtained as white crystals, mp 151—153°. *Rf* 0.55. *Anal.* Calcd. for $C_{19}H_{23}O_4N_2P$: C, 61.79; H, 4.97; N, 7.48. Found: C, 61.36; H, 5.06; N, 4.31.

Similarly, bornyl dihydrogen phosphate (**4j**) was synthesized from 0.013 molar equivalent of borneol, and it was obtained in 2.46 g (75%) as monoanilinium salt, mp 194—196°. *Rf* 0.64. *Anal.* Calcd. for $C_{16}H_{26}O_2NP$: C, 58.72; H, 8.02; N, 4.28. Found: C, 57.99; H, 8.11; N, 4.31.

[Chem. Pharm. Bull. 21(9)2070—2073(1973)]

UDC 547.732.04

Studies on Thiophene Derivatives. IX. Decarboxylation of 3-(5-Substituted 2-thienyl)malonic Acids[1]

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(Received January 8, 1973)

In our previous papers,[3,4] a number of 2-heteroaryl-3-(5-substituted 2-thienyl)acrylic acid derivatives have been reported, and the *cis* and *trans* configurations of these acrylic acids were determined by the measurement of dipole moment. Although quite a few 3-(5-substituted 2-thienyl)acrylic acids were prepared by base catalized condensations, such as Perkin reaction, Knoevenagel reaction, Reformatskiy reaction, and Wittig reaction, relatively few attempts have been made to specify the configurations of these thienyl acrylic acids.[5]

We now report the preparation and specification of the *cis*- and *trans*-3-(5-substituted 2-thienyl)acrylic acids (**3a**—**c**) and (**4a**—**c**).

Knoevenagel reactions of 5-substituted 2-thiophenecarbaldehydes (**1a**: R=H, **1b**: R=Br, and **1c**: $R=NO_2$) with malonic acid afforded the corresponding dicarboxylic acids (**2a**—**c**), which were decarboxylated in acetic anhydride at 140° to give a mixture of *cis* and *trans* acrylic acids (**3a**—**c** and **4a**—**c**). The structures and spectral data nuclear magnetic resonance (NMR), ultraviolet (UV) and infrared (IR) of these acrylic, acids which were separated by column

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1) Part VIII: H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1566 (1968).
2) Location: *1232 Komorino, Kurume, Fukuoka.*
3) H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1256 (1968).
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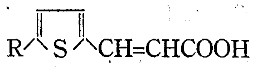
chromatography or fractional recrystallization, were shown in Table I and II. The *cis* and *trans* configrations of (**3a**—**c**) and (**4a**—**c**) were determined by the coupling constants (see Table II). All the *cis* isomers were photochemically converted to the *trans* isomers by irradiation of UV light. Meanwhile, the decarboxylation of **2c** afforded an anhydride (**5**), whose structure was confirmed by IR [bands at 1780, 1708 cm^{-1} (anhydride,[6] and 1075 cm^{-1} (ν C-O-C)[7]]. The alkaline hydrolysis of **5** afforded exclusively the *trans* acrylic acid (**4c**).

Nitration of *cis*-3-(2-thienyl)acrylic acid (**3a**) was carried out in fuming nitric acid-acetic anhydride to give a mixture of *cis* and *trans* nitrated thienyl acrylic acids (**3c** and **4c**) in 25 and 40%, respectively. The *cis* isomer obtained, which was purified by column chromatography on silica gel with benzene, was found to be identical with an authentic sample of **3c**, indicating the nitro group was introduced into the 5-position of the thiophene ring.

Table I. Physical Properties and *cis*/*trans* Ratio of 3-(5-Substituted 2-thienyl)acrylic Acids

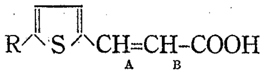


3a—**c**; **4a**—**c**

Compd.	R	mp (°C)	Appearance	*cis*/*trans* ratio	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3 a	H	136—137	colorless needles	5.0/95[a]	$C_7H_6O_2S$	54.53	3.92		54.57	3.69	
4 a	H	146—147	colorless needles		$C_7H_6O_2S$	54.53	3.92		54.25	3.76	
3 b	Br	153—155	pale yellow needles	3.5/96.5[a]	$C_7H_5O_2SBr$	35.89	2.15		35.49	2.14	
4 b	Br	209—210	pale yellow needles		$C_7H_5O_2SBr$	35.89	2.15		35.72	2.09	
3 c	NO_2	195—197	yellow prisms	2/98[b]	$C_7H_5O_4NS$	42.21	2.53	7.03	42.06	2.41	6.97
4 c	NO_2	255—256	yellow prisms		$C_7H_5O_4NS$	42.21	2.53	7.03	42.39	2.39	7.11

a) determined by gas chromatography
b) determined on the the basis of weight of each isomers

Table II. Infrared, Electronic, and Nuclear Magnetic Resonance Spectra of *cis* and *trans* 3-(5-Substituted 2-thienyl)acrylic Acids



3a—**c**; **4a**—**c**

Compd.	R	IR (KBr) cm^{-1} $\nu_{C=O}$	IR $\nu_{C=C}$	IR δ_{CH}	UV (in EtOH) λ_{max} nm	UV ε_{max}	NMR (in $CDCl_3$)[a] H_A	NMR H_B	NMR J_{AB} (cps)
3 a	H	1671	1605	824	298	8500	τ 2.72	τ 4.26	12.0
3 b	Br	1675	1610	823	310	12000	2.81	4.28	12.0
3 c	NO_2	1690	1619	821	245 355	6600 10700	2.65	3.93	12.0
4 a	H	1673	1614	976	302	15000	2.25	3.81	16.0
4 b	Br	1678	1618	980	312	19000	2.35	3.87	16.0
4 c	NO_2	1695	1623	982	246 356	7200 13700	2.25	3.45	16.0

a) TMS was used as an internal standard [60 MHz].

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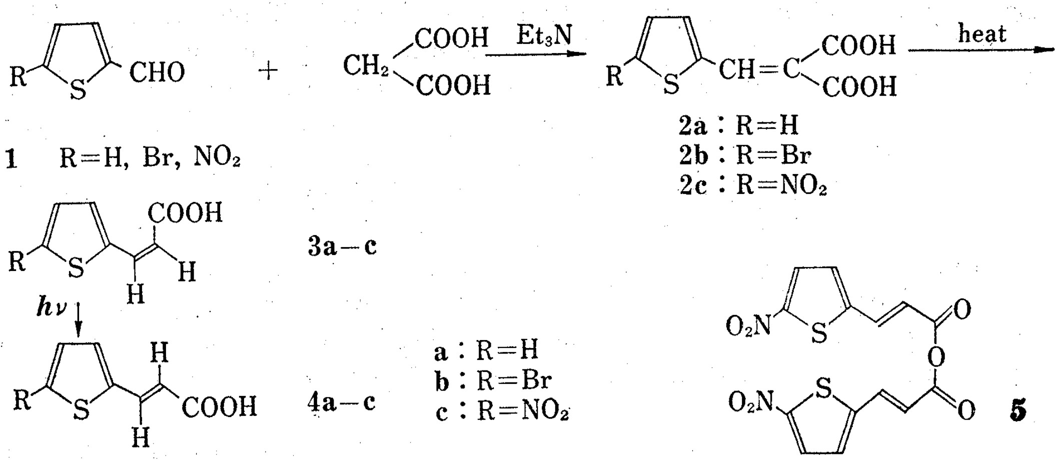

Chart 1

The *cis*/*trans* ratio of the acrylic acids described above were determined by gas chromatography, and listed in Table II. The effect of the 5-substitution on the thiophene ring was found to give a minor effect on the *cis*/*trans* ratios of the acrylic acids.

Experimental

(5-Substituted 2-thienyl)methylenemalonic Acids (2a—c)——Triethylamine (30 ml) was added dropwise to a vigorously stirred mixture of (5-substituted) 2-thiophenecarbaldehyde [**1a**: R=H, **1b**: R=Br, and **1c**: R=NO_2] (0.1 mole), malonic acid (0.1 mole) and glacial acetic acid (150 ml) at 70°. The stirring was continued for 4 hr at the same temperature, and the mixture was concentrated to a half of its volunme, and then poured into ice-chilling dil. hydrochloric acid (200 ml) to deposite the corresponding (5-substituted 2-thenyl)methylenemalonic acid (**2a**—**c**), which was filtered, washed with water, and dried (Na_2SO_4). The melting point, appearence, yield, and analytical data of these malonic acids were as follows: [**2a**: R=H, mp 221—222°, colorless needles, 12.5 g (63%). *Anal.* Calcd. for $C_8H_6O_4S$: C, 48.48; H, 3.05. Found: C, 48.69; H, 3.07]. [**2b**: R=Br, mp 196—198°, pale yellow needles, 2.40 g, yield (65%). *Anal.* Calcd. for $C_8H_5O_4SBr$: C, 34.68; H, 3.07. Found: C, 34.34; H, 1.69]. [**2c**: R=NO_2, mp 230—232°, yellow prisms, 17.5 g (72%). *Anal.* Calcd. for $C_8H_5O_6NS$: C, 39.54; H, 2.07; N, 5.76. Found: C, 39.26; H, 1.98; N, 5.54].

***cis*-and *trans*-3-(2-Thienyl)acrylic Acids (3a and 4a)**——(2-Thienyl)methylenemalonic acid (29.7 g, 0.15 mole) was suspended in acetic anhydride (30.6 g) and the mixture was refluxed for 15 minutes. After the cease of gas evolution, the reaction mixture was poured into ice-chilling dil. hydrochloric acid. Precipitating crystals were filtered, washed, dried, and recrystallized from benzene to give colorless needles, mp 146—147° (19.8 g, 85.7%). The structure of this substance was confirmed by spectral data (see Table II). The filtrate was concentrated *in vacuo* to dryness, and the residue was dissolved in a minimum amount of benzene, and chromatographed on a column of silica gel made up with benzene. The column was developed with the same solvent. After evaporation earlier fractions yielded *cis*-(2-thienyl)acrylic acid (**3a**), mp 136—137°, colorless prisms (4.3%).

***cis*-and *trans*-(5-Nitro-2-thienyl)acrylic Acid (3c and 4c)**——Decarboxylation of **2c** [R=NO_2, 29.2 g (0.12 mole)] was carried out analogously as described in the preceding procedure for **3a** and **4a**. The crude crystalline solid (22.5 g) obtained was recrystallized from ethyl acetate to give pure *trans* 3-(5-nitro-2-thienyl)acrylic acid (**4c**) (23.4 g, 97.9%), mp 255—256°. Mother liquid of the recrystallization was concentrated and cooled to give the second crystalline solid, which was purified further by chromatography (benzene). As a result, the *cis*-isomer (**3c**) was obtained as yellow prisms (0.5 g, 2.1%), mp 195—197°.

In the decarboxylation of **2c**, prolonged heating caused an inevitable dehydration of the *trans* acrylic acid to give an anhydride (**5**), mp 202—204° (from benzene). The structure of **5** was confirmed by the fact that alkaline hydrolysis gave rise excusively to *trans*-3-(5-nitro-2-thienyl)acrylic acid, which did not show depression on a mixed melting point determination with an authentic sample of **4c**. *Anal.* Calcd. for $C_{14}H_8O_7N_2S_2$: C, 44.20; H, 2.12; N, 7.36. Found: C, 44.59; H, 2.14; N, 6.97.

***cis*-and *trans*-3-(5-Bromo-2-thienyl)acrylic Acids (3b and 4b)**——The decarboxylation of **2b** [R=Br, 27.7 g (0.1 mole)] was carried out analogously as described in the preceding procedure for **3a** and **4a** and the reaction mixture was treated analogously. *trans*-3-(5-Bromo-2-thienyl)acrylic acid (**4b**) was obtained as pale yellow needles, mp 209—210° [21.3 g, 91.2%] (from benzene), and the *cis* isomer (**3b**) was purified by column chromatography on silica gel with benzene, mp 153—155°, pale yellow needles (0.7 g, 3.0%).

Nitration of *cis*-3-(2-Thienyl)acrylic Acid (3a).——To a vigorously stirred mixed acid prepared from fuming nitric acid (d=1.50, 0.8 g, 0.13 mole) and acetic anhydride (2.9 g, 0.022 mole) was added a solution of *cis*-3-(2-thienyl)acrylic acid (1.54 g, 0.01 mole) in acetic anhydride (5.1 g, 0.05 mole) dropwise at 10—15°. After the addition, the mixture was stirred further for 1 hr at the same temperature. Precipitating crystals were filtered, washed with water, and recrystallized from ethyl acetate, mp 255—256°, yellow prisms (0.5 g, 2.5%). This compound was found to be **4c** by a mixed melting point determination with an authentic sample as well as spectral data.

The acidic filtrate from which **4c** was removed by filtration was poured into ice-cold water, extracted with ethyl acetate, washed with water, and dried. On evaporation of the solvent yellow crystalline residue was obtained, which was purified by chromatography analogously as above. Evaporation of the eluate *in vacuo* gave yellow prisms of **3c** (0.8 g, 40%). A mixed melting point determination of the above product with an authentic sample of **3b** did not show a depression.

Nitration of *trans*-3-(2-Thienyl)acrylic Acid (4a)——The nitration of **4a** was carried out in a similar manner as described above. The yellow crystals were recrystallized from ethyl acetate to obtain the analytical sample of **4a**, mp 255—256° (1.4 g, 72%).

Photochemical Isomerization of *cis*-(5-Substituted 2-thienyl)**acrylic Acids** (3a—c).——A general method of photochemical isomerization was shown as follows. A solution of the *cis*-(5-substituted 2-thienyl)acrylic acid (0.05 mole) in 50 ml of ethanol was irradiated for 6—8 hr with UV lamp (Manasuru Light 3650 Å, Manasuru Kagaku Co.) at room temperature. Yields, melting points of *trans* isomers obtained are as follows: **4a**, 0.5 g (64.9%), mp 146—147°; **4b**, 0.75 g (75%), mp 209—210; **4c**, 0.85% g (71%), mp 255—256°.

The Quantitative Determination of *cis*/*trans* Ratio of the Substituted Acrylic Acids——The quantitative determinations of the *cis*/*trans* ratios were carried out by gas chromatography (Shimazu model GC-5, 2% QF-1 on chromoscorb W, 2 m×ϕ3 mm stainless column, column temp. 140°, He 50 ml/min). A mixture of *cis* and *trans* isomers of each thienylacrylic acid was esterified by diazomethane in ether and subjected to the GC-analysis. No thermal isomerization was found to occurr under the above experiment.

[Chem. Pharm. Bull.
21(9)2073—2076(1973)]

UDC 547.581.2'26.03.04

Stability of *p*-Hydroxybenzoic Acid Esters in an Acidic Medium[1]

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(Received January 19, 1973)

p-Hydroxybenzoic acid esters (parabens) have been generally used in pharmaceutical solution as preservatives.

Their stability has been mostly studied in a neutral[3,4] or alkaline solution,[3–7] and they have been considered as stable in an acidic medium.[7]

Presently a study was made of the stability of parabens in an acidic medium.

Experimental

Materials——Methyl and propyl parabens were used following recrystallization from an ethanol–water mixture. *p*-Hydroxybenzoic acid, a hydrolysate, used as standard in the quantitative determination of hydrolysate was recrystallized from an ethanol–water mixture.

Method——Methyl or propyl paraben was dissolved in 0.1 N, 0.01 N, 0.001 N, or 0.0001 N HCl solution to make a concentration of 5×10^{-4}M. Those solutions initially showed pH 1, 2, 3, and 4 respectively. Changes of pH before and after experiment were not observed except for a 0.0001 N HCl solution, of which pH changed to pH 4.3—4.5 at 40°, 60°, and 78° and to pH 5.0 at 100° after experiment.

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1) This study was supported in part by a grant of the Ministry of Public Welfare, Japan.
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