

M. Hannoun (a), N. Blazević (a), D. Kolbah (a),
A. Sabljic (b), N. Trinajstić (b),
A. Segal (c), A. Lisini (1) (c), F. Kajfež (c) and V. Šunjić (c)

(a) Department of Chemistry, Faculty of Pharmacy,
University of Zagreb, Croatia, Yugoslavia

(b) "Rugjer Bošković" Institute, P. O. B. 1016,
41001 Zagreb, Croatia, Yugoslavia

(c) Department of Biomedical and Biochemical Research, CRC,
Chemical Research Company, 33048 San Giovanni al Natisone (UD), Italy

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3-Carboxymethylbenzo[*b*]thiophenes give on benzoylation and acetylation, two pairs of isomers, **2/3** and **4/5**, respectively. It is determined by the combined nmr spectroscopic analysis (360 MHz and calculated spectra, LIS-nmr) and HOMO calculations of the electron densities on positively charged **1**, that **2** and **4** are 4-substituted, while **3** and **5** are 6-substituted isomers.

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Introduction.

In continuation of our research on some aryl- and heteroaryl-carboxylic acid derivatives as potential anti-inflammatory agents (2,3), we desired some quantities of 3-carboxy-5-benzoylbenzo[*b*]thiophenes. To this aim, Friedel-Crafts acylation of 3-carboxymethylbenzo[*b*]thiophene, separation of the isomers eventually formed, and elucidation of their structure by spectroscopic methods (high resolution and/or mass spectrometry) seemed to be an obvious approach. We encountered, however, appreciable difficulties in structure determination of the isomeric pairs, **2/3** and **4/5**. Therefore a combined approach of an LIS-nmr study of **4** and **5** and HMO calculations of the positively charged structures of the starting compound **1** was required in order to reach a conclusion concerning the position of acylation of the parent bicyclic compound.

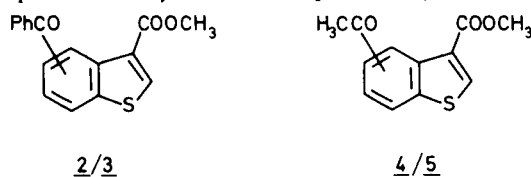


Figure 1. Isomeric Pairs **2/3** and **4/5**.

Results and Discussion.

The 360 MHz nmr spectra of **2** and **3**, as well as the 60 MHz spectra in the presence of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-praseodymium(Pr(fod)₃) shift reagent were difficult to interpret because of significant overlap of the aromatic protons. Therefore, acetylated compounds **4** and **5** were prepared under identical reaction conditions and separated on a silica gel column. The aromatic part of the 360 MHz nmr spectra of **4** and **5** indicated a trisubstituted benzene. This was confirmed by a computer simulated spectra. Proposed

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parameters for the calculated spectrum, experimental and calculated frequencies are given in Table I.

Thus, 2-substitution could be excluded in the first step of the spectra analysis. In the next step structures I or II could be proposed for compound **4** (R = Ph) and structures III or IV for compound **5** (R = Ph).

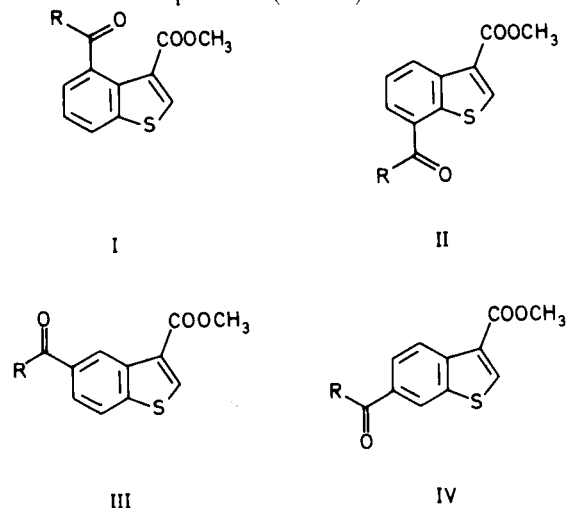


Figure 2. Proposed Structures I-IV for Compounds **4** and **5**.

The interpretation of the signals for compound **4** is the following: 7.61 ppm (t) proton in the *meta*-position to the acetyl group; 8.08 ppm (broad d) proton in the *ortho*-position to the acetyl group; 8.57 ppm (broad s) proton in the thiophene ring; 8.92 ppm (dd) proton in the *para*-position to the acetyl group.

The interpretation of the signals for compound **5** is therefore the following: 8.10 ppm (dd) proton in the *meta*-position to the acetyl group; 8.54 ppm (d) proton in the *ortho*-position to both the acetyl group and the annelated ring; 8.60 ppm (broad s) proton in the thiophene ring; 8.69 ppm (doublet) proton in the *ortho*-

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Table 1
Experimental and Calculated Frequencies of Aromatic Protons in Compounds 4 and 5

Compound 4				Compound 5			
Shifts ppm	Coupling constants (a)	Frequencies (a,b)		Shifts ppm	Coupling constants (a)	Frequencies (a,b)	
		Calcd.	Expt.			Calcd.	Expt.
Hc 7.61	$J_{c,b}$ 8.40	3189.36	3189.31	Hb 8.10	$J_{b,c}$ 8.33	3110.63	
Hb 8.08	$J_{c,d}$ 7.52	3188.45	3188.42	Hd 8.54	$J_{d,c}$ 1.30	3110.13	3110.53
Ha 8.57	$J_{b,d}$ 0.9	3180.96	3181.35	Ha 8.60	$J_{b,d}$ 0.50	3102.30	
Hd 8.92		3180.06	3180.02	Hc 8.69		3101.80	3101.73
		3061.05	3061.05			3073.43	3073.43
		2891.50				3052.68	
			2890.70				3052.20
		2890.59				3052.18	
		2883.98				3051.35	
			2883.69				3051.32
		2883.07				3050.85	
		2730.09	2729.78			2899.27	2899.61
		2722.57				2897.94	2897.84
		2721.70	2722.26			2890.95	2890.77
		2714.18	2713.85			2889.62	2889.44

(a) Values in Hz. (b) From TMS as the standard.

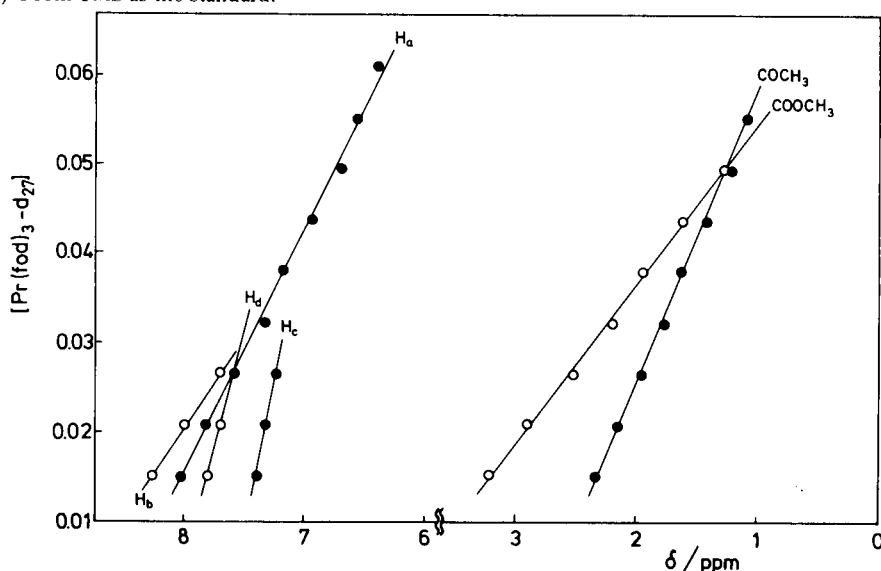


Figure 3. Dependence of the LIS Induced Shifts on the Molar Concentration of the $\text{Pr}(\text{fod})_3\text{-d}_{27}$ for Various Groups of Protons in Compound 4.

position to the acetyl group.

Since long-range coupling constants between the proton in the thiophene ring and the other aromatic protons were not visible in the actual spectra, the structures for 4 and 5 could not be unequivocally established. Therefore, LIS-measurements were performed using $\text{Pr}(\text{fod})_3$ as the shift reagent. The results are represented in Figures 3 and 4.

The induced shifts of the various protons in 4 and 5 offered the following information: (a) The binding site of the lanthanide in the complex with both 4 and 5 should be primarily a ketone carbonyl oxygen. This is in accordance with the order found generally for the series of the oxygen hard and soft basis (4,5). The recent data suggest

a general preference of complexation at the carbonyl group rather than at sulphur (6). (b) The methyl group CH_3CO , and the protons *ortho*- to the acetyl moiety in compound 5 (Hc, Hd) are shifted the most. In compound 4, however, the methoxy group possesses the highest induced shift of all of the protons, which indicates that the carboxymethyl group is a second binding site, *i.e.* demonstrating the bidentate nature of 4 as the ligand. Such binding could be realized only if the isomeric structure I is present in 4; the shifts for protons Ha, Hb and Hc are in accordance with this structure. Isomer 5, however, reveals a low slope of the methoxy group. These data exclude the structure III, where there is the possibi-

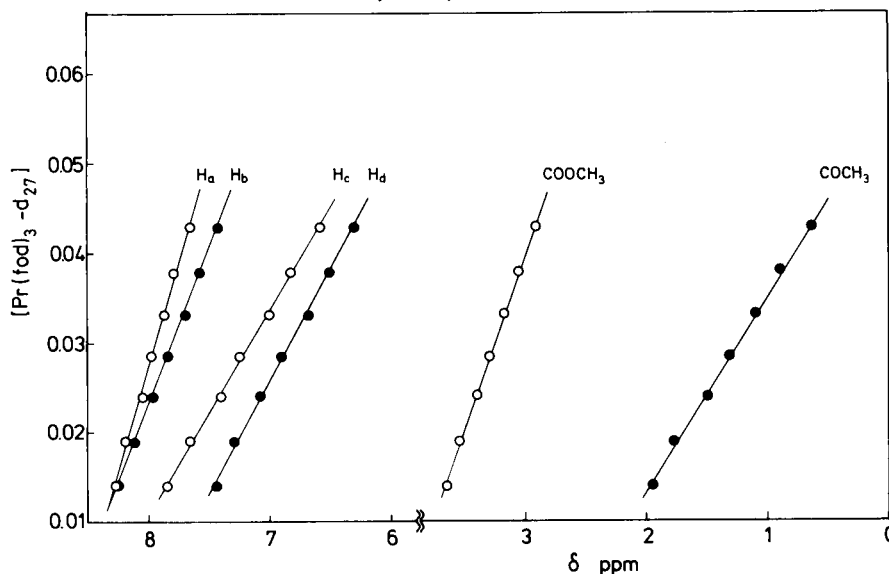


Figure 4. Dependence of the LIS Induced Shifts on the Molar Concentration of the $\text{Pr}(\text{fod})_3\text{-d}_{27}$ for Various Groups of Protons in Compound **5**.

lity for bidentate binding of the lanthanide in one of the four possible all-planar conformations. The structure IV for compound **5** is thus confirmed.

The structure assignment based on the nmr data analysis has been supported by HOMO (7) calculations of the electron densities for the substrate **1**. They should indicate preferred sites for electrophilic Friedel-Crafts acylation.

The MO approach used herein was deduced from the early work of Dewar and Trinajstić (8). They used the SCF MO π method (9) to calculate ground state properties of compounds containing σ -bivalent sulfur. Their result for the π -electron density of benzo[*b*]thiophene, shown in the Figure 5, suggests that electrophilic substitution will take place at position 3, because of the greatest π -electron density. This was also confirmed experimentally (10).



Figure 5. Calculated π -Electron Densities for Benzo[*b*]thiophene (8) and 3-Carboxymethylbenzo[*b*]thiophene (Case 4 from Table 2).

In this work our major interest was at which position the second electrophilic substitution takes place, when position 3 of benzo[*b*]thiophene is already occupied by an electron-withdrawing group (COOCH_3). We have used the simple HOMO method with parameters recommended by Streitwieser (11) in order to calculate π -electron densities of compound **1**. Parameters and results of calculation are presented in Table 2, Case 1. From these results we can predict using the isolated molecule approximation model (12) that the second electrophilic substitution will most probably take place at positions 5 and 7. However,

Table 2

Predicted Positions and Parameters used for Second Electrophilic Substitution of Variously Charged Benzo[*b*]thiophenes

Case	H. S	k S-C ₂	k S-C _{7a}	Predicted positions
1	1.0	0.5	0.5	7, 5
2	4.0	0.5	0.5	7, 4
3	1.5	0.3	0.3	4, 7
4	1.5	0.4	0.3	4, 6

this was shown to contradict the experimental findings.

During Friedel-Crafts acylation, compound **1** should coordinate in the acid-base complex with aluminum chloride as a Lewis acid. In such a complex, a partial positive charge at the sulfur atom emerges (13). Consequently, the nonbonding-electron pair is more localized on the sulfur atom and the π -character of the two C-S bonds is decreased. Thus, in the next step we investigated the positively charged structure **1** using three different groups of adapted parameters for sulfur and two C-S bonds. Parameters and results for π -electron densities are given in Table 2 and Figure 5.

In the first case, the positive charge on the sulfur atom is simulated by increasing the "h" parameter for sulfur. Enormous enlargement of that parameter will change the positions with the greatest π -electron density (positions 4 and 7). These results were still in disagreement with experimental findings.

In the second and the third cases, besides enlargement of the "h" parameter, the π -character of the two C-S bonds is decreased symmetrically and unsymmetrically. Only the calculated results of the third case coincide with experimental data. This simple numerical analysis indi-

Table 3
HOMO π -Values and Reactivities of some Benzo[*b*]thiophenes

Compound	HOMO (in β)	Experimental Conditions	Yields (%)
Benzo[<i>b</i>]thiophene	0.6063	room temperature, aluminum chlorides 24 hours	38% 38% (reference 10)
3-Carboxymethylbenzo[<i>b</i>]thiophene	0.6585	Boiling temperature of carbon disulfide, aluminum chloride, 6 hours	36% (reference 16)
3-Acetylbenzo[<i>b</i>]thiophene	0.6715	200°, aluminum chloride, 10 hours	0% (reference 16)

cated that the second electrophilic substitution would take place at positions 4 and 6, favoring the former which has the greatest π -electron density among all positions which are available for substitution. In fact, electrophilic substitution of compound **1** resulted in a 3:1 mixture of the 4- and 6-positional isomers.

Our further investigation was directed to determine the influence of 3-substitution in benzo[*b*]thiophene on reactivity of the resulting substituted compounds towards electrophilic substitution. Electrophilic substitution may be viewed as a donor-acceptor interaction in which an electrophilic-donor transfers its electrons from its highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electrophile (14).

In our case, we always have the same electrophile, *i.e.* benzoyl chloride, and its LUMO level will always be the same. Thus, the reactivity of benzo[*b*]thiophenes towards electrophilic substitution will be directly proportional to the energy of the HOMO levels.

By application of the generalized perturbation treatment (15) one finds that the transfer of charge to the LUMO level of an acceptor is facilitated; enhanced electrophilic reactivity may be observed the higher the HOMO level of the electrophilic donor is. In Table 3 our HOMO results for the HOMO level of benzo[*b*]thiophenes are compared with yields and experimental conditions under which electrophilic substitution takes place.

From the Table 3 it can be seen that the benzo[*b*]thiophene possessing the highest HOMO level undergoes electrophilic substitution under mild conditions and gives the highest yield of product (10). Compound **1**, possessing the lower HOMO level, needs much more severe reaction conditions and the yield of product is poorer than in the former case (16). 3-Acetylbenzo[*b*]thiophene has the lowest HOMO level among all of the examined compounds; consequently, experimental conditions for electrophilic substitution are most severe and the yield of product is very poor.

In conclusion it can be demonstrated that with stronger electron-withdrawing group attached to benzo[*b*]thiophene, the resulting compound will show a lower reactivity towards electrophilic substitution.

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage (Boettius). IR spectra were run on a Perkin Elmer M 297 spectrometer as potassium bromide pellets unless otherwise stated. Nmr spectra were obtained and LIS-experiments were performed on a Perkin Elmer R 12 spectrometer. The shift reagent Pr(fod)₃d₂₇ was sublimed prior to use and deuteriochloroform was stored over molecular sieves (4 Å). Column chromatography was performed on a silica gel 70-230 mesh (Merck), while the control of the fractions was performed using silica gel precoated aluminium plates F₂₅₄ (Merck). All solvents were dried over sodium sulfate and evaporated *in vacuo*.

Benzo[*b*]thiophene-3-carboxylic acid has been prepared in 62% yield by decarboxylation of benzo[*b*]thiophene-2,3-dicarboxylic acid (17), according to the described procedure (18). 3-Carboxymethylbenzo[*b*]thiophene (1).

This compound was obtained on esterification of the acid (11.2 g., 63 mmoles), performed in methanol (250 ml.) which contained sulfuric acid (3% by volume). After 4 hours of heating under reflux, the solvent was partially evaporated. The residue was then poured onto ice-water and extracted with ether (3 x 100 ml.). After drying and evaporation, the residual oil was distilled at 95°/0.5 mm (lit. (19) b.p. 165-166°/17 mm), to afford 8.7 g. (70%) of pure **1**; ir (film): 3010, 1705, 1600, 1515, 1470, 1440, 1380, 1220, 1065, 1040, 922, 860, 800, 740, 720 cm⁻¹; nmr (deuteriochloroform): δ 3.93 (s, 3H), 7.20-7.60 (m, 2H), 7.75-7.95 (m, 1H), 8.33 (s, 1H), 8.48-8.82 (m, 1H) ppm. Benzoylation of **1**.

To the compound **1** (3.84 g., 2.0 mmoles) dissolved in carbon disulfide (20 ml.) and stirred and cooled with ice-water, aluminum chloride (19.0 g., 140 mmoles) was added in small portions. The reaction mixture was stirred at room temperature for 20 minutes, after which time benzoyl chloride (14.0 g., 10 mmoles) dissolved in carbon disulfide (30 ml.) was added dropwise. After stirring for 60 minutes at room temperature, the reaction mixture was heated under reflux for 10 hours. The cooled solution was decanted from the residual paste which was treated with ice-water and extracted with ether (3 x 100 ml.). The ethereal extracts were washed with

ether (3 x 100 ml.). The ethereal extracts were washed with 10% aqueous sodium bicarbonate, dried and evaporated. The residual oil crystallized from ether-light petroleum. Thus, 1.7 g. (28%) of pure **2** were obtained, m.p. 115-117°. Recrystallization from the same solvent mixture gave m.p. 118-119°; ir: 1719, 1670, 1600, 1505, 1460, 1360, 1320, 1280, 1220, 1200, 1040, 970, 760, 710 cm^{-1} ; nmr (deuteriochloroform): δ 3.98 (s, 3H), 7.3-7.6 (m, 5H), 7.75-8.1 (m, 3H), 8.2-8.3 (s, 1H) ppm.

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_3\text{S}$ (296.35): C, 68.90; H, 4.08; S, 10.82. Found: C, 69.16; H, 4.22; S, 10.49.

Compound 3.

This compound was obtained from the mother liquors after crystallization of **2**. On evaporation it was purified by column chromatography using the solvent mixture benzene-light-petroleum-acetone (1:1:0.25) as eluent. Thus, 0.5 g. (8%) of **3**, m.p. 104-105° (from ether-light petroleum) were obtained, ir: 1705, 1643, 1600, 1500, 1443, 1405, 1376, 1312, 1300, 1223, 1035, 945 cm^{-1} ; nmr (deuteriochloroform): δ 3.96 (s, 3H), 7.4-7.7 (m, 3H), 7.74-8.1 (m, 3H), 8.25-8.45 (s, 1H), 8.5-8.8 (m, 2H) ppm.

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_3\text{S}$ (296.35): C, 68.90; H, 4.08; S, 10.82. Found: C, 69.13; H, 4.28; S, 10.76.

Acetylation of 1.

Acetylation was performed using 8.0 g. (0.041 mmoles) of **1** dissolved in carbon disulfide (150 ml.). The solution was cooled in an ice bath; 8.0 g. (0.06 mole) aluminum chloride were added followed during the next 30 minute period with 5.0 g. (0.064 mole) of acetyl chloride dissolved in carbon disulfide (20 ml.), which was added dropwise. The reaction mixture was refluxed for 16 hours and cooled to room temperature; the carbon disulfide was decanted and evaporated *in vacuo*. The residue were treated with water and extracted with ether (3 x 25 ml.). The ethereal extracts were combined, dried and evaporated to dryness. The oily material obtained was purified by column chromatography using the solvent mixture benzene:acetone:light petroleum (20:1:20) as eluent. Two isomers were obtained with the total yield being 5.85 g. (60%). The first-running isomer **5** had m.p. 121-123°, yield 1.95 g.; the second (**4**) had m.p. 151-153°, yield 3.90 g.

Compound **4** had m.p. 151-153°; nmr (deuteriochloroform): δ 2.70 (s, 3H), 4.00 (s, 3H), 8.02 and 8.16 (dd, 2H), 8.5-8.8 (m, 3H) ppm.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_3\text{S}$ (234.27): C, 61.52; H, 4.30; S, 13.68. Found: C, 61.37; H, 4.32; S, 13.85.

Compound **5** had m.p. 121-123°; nmr (deuteriochloroform): δ (s, 3H), 3.96 (s, 3H), 7.6-9.0 (m, 4H) ppm.

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_3\text{S}$ (234.27): C, 61.52; H, 4.30; S, 13.68. Found: C, 61.83; H, 4.38; S, 13.90.

Computer calculations were performed on UNIVAC 1110 at the University of Zagreb Computer Centre.

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