116. (Benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)acetic Acids: Novel Non-ulcerogenic Antiinflammatory Agents

by **Pietro Bollinger**[a]), **Philip Cooper**[b]), **Hans U. Gubler**[b]), **Albert Leutwiler**[b])*, and **Trevor Payne**[b])

[a]) Preclinical Research, *Sandoz Pharma Ltd.*, CH-4002 Basel
[b]) *Sandoz Research Institute*, P.O. Box 2173, CH-3001 Bern

(7.V.90)

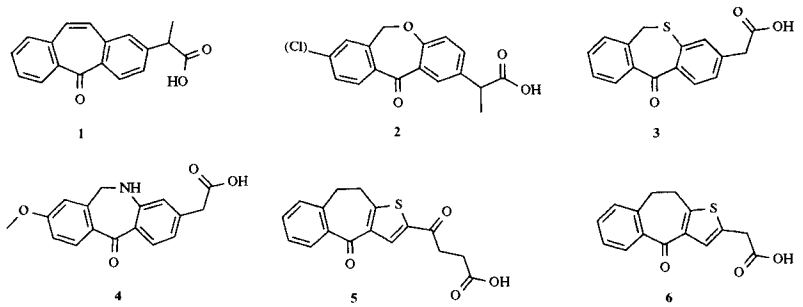
Compound (*Z*)-**8a** has been found to display interesting antiinflammatory activity. In order to prepare derivatives with a wide variety of substituents in the aromatic part of the molecule, a new synthesis of the key intermediates **9a–g** was developed starting from thiophene-3-carboxylic acid (**11**) and substituted benzyl bromides. The conversion of **9a–g** to **10a–g** follows a known procedure. Ketones **10a–g**, on reaction with alkyl (dialkoxyphosphoryl)acetate, followed by isomer separation and alkaline ester hydrolysis, yielded the desired derivatives (*Z*)-**8a–g** and (*E*)-**8a–g**. The biologically most interesting compound (*Z*)-**8a** is currently undergoing clinical trials.

1. Introduction. – The inflammatory diseases rheumatoid arthritis, osteoarthritis, and gouty arthritis usually are treated with one of the many nonsteroidal antiinflammatory drugs currently available. In particularly severe and refractory cases, corticosteroids in oral or intra-articular form are used [1]. Neither of these therapies is fully satisfactory because of the wide range of disturbing side effects such as gastrointestinal irritation, bleeding, and ulceration [2].

Other drugs usually used only for refractory cases of rheumatoid arthritis include D-penicillamine, gold derivatives, and cytotoxic drugs. All of them produce serious side effects [3] which greatly restrict their clinical use. A better alternative is clearly required.

Our goal was to find a new antirheumatic/antiphlogistic agent which fulfils the following criteria: *i*) it should have a new mechanism of action not depending on cyclooxygenase inhibition, *ii*) it should modify the course of the disease and not just produce symptomatic improvement (*i.e.* it should prevent progressive joint destruction), *iii*) it should possess analgetic as well as antiphlogistic activity, and *iv*) it should lack severe side effects.

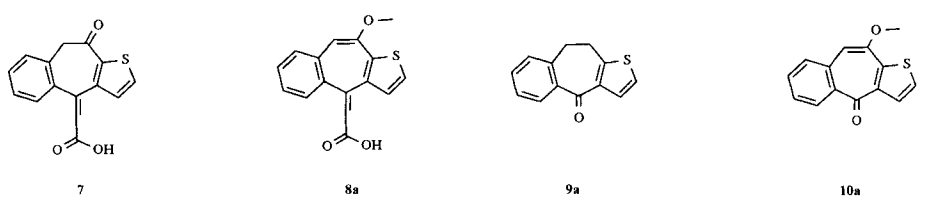
From previous work (both in our laboratories and by others), it was known that many tricyclic compounds having two aromatic rings grouped around a central seven-membered ring display potent analgetic and antiinflammatory activities. These include dibenzotropone **1** [4], dibenzoxepines **2** [5], dibenzothiepine **3** [6], and dibenzazepine **4** [7], all bearing an acetic-acid side chain and showing moderate to strong inhibition of cyclooxygenase. Moreover, it was found in our laboratories that the 9,10-dihydro-4*H*-benzo[4,5]-cyclohepta[1,2-*b*]thiophene derivative **5**, in contrast to compounds **1–4**, does not inhibit prostaglandin synthesis *in vitro* and yet is a moderate to strong inhibitor of the developing and fully established *Freund* adjuvant induced arthritis of the rat. Furthermore, **5** does not inhibit blood platelet aggregation *in vivo* and is devoid of antipyretic activity. It was



later found that, *in vivo*, **5** is metabolized to the corresponding (heteroaryl)acetic acid **6**, a weak inhibitor of prostaglandine (PG) synthesis which showed a pharmacological profile, including ulcerogenicity, similar to other cyclooxygenase inhibitors.

Although **5** did not fulfil all our requirements, its exceptionally good tolerance compared with its antiarthritic activity suggested that the observed biological activity may not only be a consequence of cyclooxygenase inhibition. It was, therefore, postulated that another mechanism of action could be operative in addition to inhibition of prostaglandin biosynthesis. Further chemical derivation was, therefore, undertaken to see if the activity in models of chronic inflammation could be separated from cyclooxygenase inhibition.

2. Results and Discussion. – a) *New Benzocycloheptathiophene Derivatives.* The (heteroarylidene)acetic acid **7** was planned as part of a series of different derivatives of **5** lacking the structure-activity relationships required for cyclooxygenase inhibition [8–11]. Compound **7** incorporates a cyclic-ketone function, as this group was essential for biological activity in the lead compound, but lacks a (*Z*)-dec-4-enoic-acid unit [12] or a [3-(arylcarbonyl)phenyl]acetic-acid equivalent which are characteristics of many cyclooxygenase inhibitors [9].

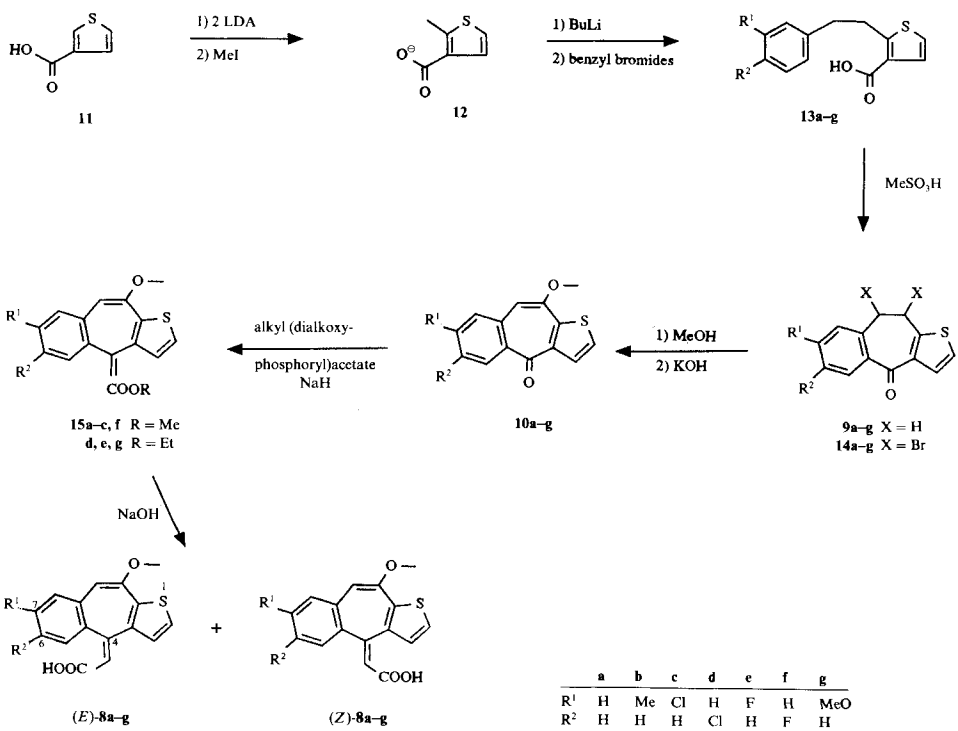


The synthesis of a number of functionalized benzo[4,5]cyclohepta[1,2-*b*]thiophene derivatives starting from **9a** [13] was well known from previous work in our laboratories [14]. The acrylic-acid functionality in **7** was introduced by a *Horner* reaction on the methoxy ketone **10a** [14]. Subsequent basic hydrolysis of the ester group followed by acidic hydrolysis of the enol-ether group led to the desired product **7**. As had been hoped for, compound **7** showed at least some weak antiphlogistic activity without cyclooxygenase inhibition. To our surprise, the intermediate enol ether **8a** showed significantly higher antiphlogistic activity than **7** and still was devoid of cyclooxygenase inhibitory activity.

This finding prompted us to separate the (*E*/*Z*)-mixture **8a** into the pure (*Z*)- and (*E*)-isomers. The more potent (*Z*)-isomer, unlike known antiinflammatory agents of similar potency, proved to be devoid of ulcerogenic activity suggesting that a novel mechanism of action was responsible for the antiphlogistic activity. The (*E*)-isomer, on the other hand, was ulcerogenic. Based on these results, we decided to design and synthesize a series of substituted derivatives of **8a**.

b) *Alternative Synthetic Route to (Benzocycloheptathiophenylidene)acetic Acids* (see *Scheme*). Our primary target was the synthesis of intermediates **9b–g** which were pivotal in the preparation of the desired compounds **8b–g**. To achieve high variability for substituents R^1 and R^2 in the aryl part of **9**, we did not follow the known synthetic route [13], but developed a new synthesis starting from the commercially available thiophene-3-carboxylic acid (**11**), MeI, and substituted benzyl bromides *(Scheme)*. Treatment of **11** with 2 equiv. of lithium diisopropylamide (LDA) in abs. THF at – 78° produced a dianion [15] which was reacted with 1 equiv. of MeI for 1 h to give, after a slow temperature increase to 15°, the anion **12** of 2-methylthiophene-3-carboxylic acid [16]. Subsequent reaction with 1 equiv. of BuLi at – 78° (→dianion of **12**) and 1 equiv. of the desired substituted or unsubstituted benzyl bromide for 2 h at 0° yielded the 2-(arylethyl)thiophene-3-carboxylic acids **13a–g**. The crude products were cyclized by stirring in $MeSO_3H$ at elevated temperature to give the tricyclic ketones **9a–g** with overall yields of *ca.* 40% after purification. This procedure proved to be very efficient.

Scheme



The conversion of ketones **9a–g** to the desired 10-methoxy-substituted ketones **10a–g** was achieved following the described procedure (bromination followed by treatment with MeOH and KOH) [14], and reaction of ketones **10a–g** with alkyl (dialkoxyphosphoryl)acetates (*Horner-Emmons* reaction) gave the (*E*/*Z*)-mixtures **15a–g**. The isomers were separated by column chromatography (silica gel) and subsequently hydrolyzed to the corresponding (heteroarylidene)acetic acids **8a–g**. In each case, the configuration of the double bond was assigned by NOE experiments of the acid or the corresponding ester.

c) *Biological Results and Discussion.* In general, the antiinflammatory activity of the compounds was assessed in the therapeutic *Freund* adjuvant arthritis assay [17], a test which has been used for many years to screen for agents that could be of therapeutic value in rheumatoid arthritis [20]. *In vitro* activity against cyclooxygenase from bovine seminal vesicles was measured in order to exclude compounds acting *via* this mechanism. On interesting compounds, further tests were undertaken to demonstrate that the agents were not pro-drugs of cyclooxygenase inhibitors *in vivo*. Therefore, ulcerogenicity was determined following the daily administration of the compounds to rats having free access to food and water, over a period of 5 days. Failure to produce stomach ulceration indicates that the compounds are unlikely to be cyclooxygenase inhibitors or prodrugs of these.

From the pharmacological results in the *Table*, it can be seen that (*Z*)-**8a**, (*Z*)-**8c**, and (*E*/*Z*)-**8e** are the most interesting compounds. Activity generally resides in the (*Z*)-isomer. Substituents in the benzo moiety other than a Cl- and F-atom at the 7 position (R^1), lead to loss of activity. The 7-Cl substituent (**8c**) increases antiinflammatory potency but, at the same time, cyclooxygenase inhibitory potency and ulcerogenicity are also increased.

Table. *Antiinflammatory Activity of (Benzocycloheptathiophenylidene)acetic Acids*

	COX[a]) IC_{50} (μM)	AA[b]) ED_{50} (mg/kg *p.o.*)	Ulcerogenicity UD_{50} (mg/kg *p.o.*)
7	> 100	> 30 (–27)	
8	> 100	24	
(*Z*)-**8a**	> 100	14	> 500
(*E*)-**8a**	> 100	> 20 (–21)	250
(*Z*)-**8b**	> 100	20	
(*E*)-**8b**	> 100	> 20 (–36)	
(*Z*)-**8c**	40	6	200–300
(*E*)-**8c**	> 100	25	> 100
(*Z*)-**8d**	> 100	> 20 (–32)	
(*E*)-**8d**	> 100	> 20 (–20)	
(*E*/*Z*)-**8e**	> 100	10	> 100
(*Z*)-**8f**	> 100	> 20 (–33)	
(*E*)-**8f**	> 100	> 20 (–42)	
(*Z*)-**8g**	> 100	> 20 (–9)	
(*E*)-**8g**	> 100	> 20 (–14)	
Voltaren	0.3	3	6
Sandimmun	> 100	10	> 100

[a]) COX = Cyclooxygenase inhibition.
[b]) AA = Adjuvans arthritis inhibition.

The most interesting compound of this series is (*Z*)-**8a** which seems to fulfil most of the requirements we had set ourselves for a new antirheumatic drug. The full pharmacological profile of this compound will be reported in detail elsewhere. Some initial clinical results with (*Z*)-**8a** have recently appeared [19]. Compounds of this class clearly represent a new type of antirheumatic drug. Their exact mechanism of action remains unclear, although some findings implicating inhibition of cytokine release have been reported [20].

Experimental Part

General. The reactions were routinely carried out under dry Ar, and yields refer to non-optimized reaction conditions. M.p.: hot-stage microscope. TLC: 0.25 mm precoated silica-gel plates (silica gel *60* F_{254}, *Merck*). Flash chromatography (FC) [21] and medium-pressure liquid chromatography (MPLC): *Merck* silica gel *60* (0.04–0.063 mm). ^{1}H-NMR spectra: *Bruker-WP80-CW* (80 MHz), *Varian-Gemini* (200 MHz) or *Bruker-WH360* (360 MHz) spectrometer.

2-(2-Phenylethyl)thiophene-3-carboxylic Acid (**13a**). To a soln. of (i-Pr)$_2$NH (17 ml, 0.12 mol) in dry THF (170 ml), 1.6M BuLi in hexane (50 ml, 0.08 mol) was added dropwise at – 78°. After 30 min, a soln. of thiophene-3-carboxylic acid (**11**; 5.1 g, 0.04 mol) in THF (20 ml) was added dropwise with stirring at – 78°. Stirring at – 78° was continued for 45 min, and then MeI (2.8 ml, 0.045 mol) was added. The mixture was stirred for 1 h without cooling, the temp. then lowered to – 78° again and BuLi (25 ml, 0.04 mol) added. The cooling bath was replaced by an ice-bath, a soln. of benzyl bromide (5.4 ml, 0.045 mol) in dry THF (20 ml) added ($T \leq 3°$), and the mixture stirred for 2 h at 0°. H_2O (50 ml) was added and THF distilled off at reduced pressure. The residue was partitioned between Et_2O (700 ml) and H_2O, the aq. phase separated, acidified with 4N HCl, and extracted with AcOEt, and the org. layer washed with brine, dried (Na_2SO_4), and evaporated: 7.8 g (84%) of **13a** as a yellow oil which was used without further purification for the next step. ^{1}H-NMR (80 MHz, $CDCl_3$): 2.8–3.2 (*m*, 3 H); 3.4–3.7 (*m*, 2 H); 6.8–7.6 (*m*, 7 H); 9.6 (br., 1 H).

Analogously, **13b–g** were prepared using substituted benzyl bromides.

2-[2-(3-Methylphenyl)ethyl]thiophene-3-carboxylic Acid (**13b**; 89%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.28 (*s*, 3 H); 2.8–3.2 (*m*, 2 H); 3.3–3.7 (*m*, 2 H); 6,8–7.3 (*m*, 5 H); 7.43 (*d*, *J* = 5.5, 1 H); 11.07 (br., 1 H).

2-[2-(3-Chlorophenyl)ethyl]thiophene-3-carboxylic Acid (**13c**; 81%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.8–3.2 (*m*, 2 H); 3.3–3.7 (*m*, 2 H); 6.9–7.3 (*m*, 5 H); 7.47 (*d*, *J* = 5.5, 1 H); 9.3 (br., 1 H).

2-[2-(4-Chlorophenyl)ethyl]thiophene-3-carboxylic Acid (**13d**; 74%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.6–3.0 (*m*, 2 H); 3.1–3.5 (*m*, 2 H); 6.7–7.5 (*m*, 6 H); 8.5 (br., 1 H).

2-[2-(3-Fluorophenyl)ethyl]thiophene-3-carboxylic Acid (**13e**; 84%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.8–3.2 (*m*, 2 H); 3.3–3.7 (*m*, 2 H); 6.6–7.6 (*m*, 6 H); 11.65 (br., 1 H).

2-[2-(4-Fluorophenyl)ethyl]thiophene-3-carboxylic Acid (**13f**; 92%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.8–3.2 (*m*, 2 H); 3.3–3.7 (*m*, 2 H); 6.7–7.35 (*m*, 5 H); 7.45 (*d*, *J* = 5.5, 1 H); 11.47 (br., 1 H).

2-[2-(3-Methoxyphenyl)ethyl]thiophene-3-carboxylic Acid (**13g**; 88%): ^{1}H-NMR (200 MHz, $CDCl_3$): 3.0 (*t*, *J* = 8.0, 2 H); 3.5 (*t*, *J* = 8.0, 2 H); 3.77 (*s*, 3 H); 6.7–6.9 (*m*, 2 H); 7.04 (*d*, *J* = 5.0, 1 H); 7.2 (*m*, 1 H); 7.47 (*d*, *J* = 5.0, 1 H).

9,10-Dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one (**9a**). Crude **13a** (2.3 g, 0.01 mol) in $MeSO_3H$ (18 ml) was stirred at 110° for 2 h. The dark soln. was poured onto crushed ice and extracted with EtO. The org. layer was washed successively with H_2O, 2N Na_2CO_3, and brine, dried (Na_2SO_4), and evaporated. FC (toluene) gave 0.7 g (33%) of **9a** as a dark oil. ^{1}H-NMR (80 MHz, $CDCl_3$): 3.18 (*s*, 4 H); 6.96 (*d*, *J* = 5.5, 1 H); 7.1–7.5 (*m*, 3 H); 7.63 (*d*, *J* = 5.5, 1 H); 7.9 (*m*, 1 H).

Following the above procedure **9b–g** were prepared.

9,10-Dihydro-7-methyl-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one (**9b**; 68%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.34 (*s*, 3 H); 3.15 (*s*, 4 H); 6.8–7.4 (*m*, 3 H); 7.62 (*d*, *J* = 5.5, 1 H); 7.84 (*d*, *J* = 8.0, 1 H).

7-Chloro-9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one (**9c**; 31%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.18 (*s*, 4 H); 6.99 (*d*, *J* = 5.5, 1 H); 7.1–7.5 (*m*, 2 H); 7.62 (*d*, *J* = 5.5, 1 H); 7.90 (*d*, *J* = 8.0, 1 H).

6-Chloro-9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-one (**9d**; 40%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.15 (*s*, 4 H); 6.98 (*d*, *J* = 5.5, 1 H); 7.05–7.5 (*m*, 2 H); 7.60 (*d*, *J* = 5.5, 1 H); 7.88 (*d*, *J* = 2.0, 1 H).

*7-Fluoro-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**9e**; 30%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.16 (*s*, 4 H); 6.7–7.4 (*m*, 3 H); 7.61 (*d*, *J* = 5.5, 1 H); 7.96 (*m*, 1 H).

*6-Fluoro-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**9f**; 17%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.18 (*s*, 4 H); 6.7–7.4 (*m*, 3 H); 7.5–7.8 (*m*, 2 H).

*9,10-Dihydro-7-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**9g**; 47%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.15 (*s*, 4 H); 3.80 (*s*, 3 H); 6.6–7.1 (*m*, 3 H); 7.63 (*d*, *J* = 5.5, 1 H); 7.98 (*d*, *J* = 8.4, 1 H).

*9,10-Dibromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**14a**) was synthesized as described [14]. Using the same procedure, **14b–g** were prepared. All compounds **14** were used for the next step as crude products.

*10-Methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10a**) was prepared in 43% yield as described [14] starting from **14a**. M.p. 164–165°. ^{1}H-NMR (80 MHz, $CDCl_3$): 3.95 (*s*, 3 H); 6.45 (*s*, 1 H); 7.3–7.8 (*m*, 4 H); 7.96 (*d*, *J* = 5.5, 1 H); 8.60 (*m*, 1 H).

Using the same procedure, **10b–g** were prepared.

*10-Methoxy-7-methyl-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10b**; 45%): M.p. 142–143°. ^{1}H-NMR (80 MHz, $CDCl_3$): 2.41 (*s*, 3 H); 3.93 (*s*, 3 H); 6.37 (*s*, 1 H); 7.1–7.5 (*m*, 3 H); 7.95 (*d*, *J* = 5.5, 1 H); 8.51 (*d*, *J* = 9.0, 1 H).

*7-Chloro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10c**; 44%): M.p. 217–219°. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.0 (*s*, 3 H); 6.38 (*s*, 1 H); 7.3–7.6 (*m*, 3 H); 7.97 (*d*, *J* = 5.5, 1 H); 8.56 (*d*, *J* = 8.5, 1 H).

*6-Chloro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10d**; 58%): M.p. 218–220°. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.0 (*s*, 3 H); 6.46 (*s*, 1 H); 7.3–7.6 (*m*, 3 H); 7.96 (*d*, *J* = 5.5, 1 H); 8.58 (br., 1 H).

*7-Fluoro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10e**; 40%): M.p. 196–197°. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.01 (*s*, 3 H); 6.40 (*s*, 1 H); 7.0–7.6 (*m*, 3 H); 7.98 (*d*, *J* = 5.5, 1 H); 8.65 (*m*, 1 H).

*6-Fluoro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10f**; 38%): M.p. 212–214°. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.0 (*s*, 3 H); 6.52 (*s*, 1 H); 7.1–7.8 (*m*, 3 H); 7.97 (*d*, *J* = 5.5, 1 H); 8.35 (*m*, 1 H).

*7,10-Dimethoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one* (**10g**; 20%): M.p. 176–180°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.95 (*s*, 3 H); 4.03 (*s*, 3 H); 6.46 (*s*, 1 H); 6.9–7.2 (*m*, 2 H); 7.45 (*d*, *J* = 5.5, 1 H); 8.02 (*d*, *J* = 5.5, 1 H); 8.65 (*d*, *J* = 8.5, 1 H).

*Methyl (10-Methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)acetate* (**15a**). To a suspension of NaH (1.8 g, 80% in white oil; 0.06 mol) in DMSO (55 ml) was added dropwise methyl (dimethoxyphosphoryl)acetate. The mixture was stirred for 30 min at r.t., then **10a** (8.0 g, 0.033 mol) in DMF (80 ml) was added at once. The resulting mixture was stirred at 90° for 15 h, then poured on crushed ice (2 kg) and extracted 3 times with 1 l of AcOEt. The combined org. layers were washed 3 times with H_2O and 3 times with brine, dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2) gave 7.6 g of **15a** (77%) as an (*E*/*Z*)-mixture. By MPLC, (cyclohexane/AcOEt 20:1) 7.6 g **15a** were separated into 4.4 g (45%) of (*Z*)-**15a** and 2.4 g (24%) of (*E*)-**15a**. (*Z*)-**15a**: ^{1}H-NMR (360 MHz, $CDCl_3$): 3.64 (*s*, 3 H); 3.89 (*s*, 3 H); 5.90 (*s*, 1 H); 6.15 (*s*, 1 H); 7.08 (*d*, *J* = 5.5, 1 H); 7.25–7.37 (*m*, 4 H); 7.4–7.46 (*m*, 1 H).(*E*)-**15a**: ^{1}H-NMR (360 MHz, $CDCl_3$): 3.59 (*s*, 3 H); 3.89 (*s*, 3 H); 5.96 (*s*, 1 H); 6.22 (*s*, 1 H); 7.10 (*d*, *J* = 5.5, 1 H); 7.2–7.4 (*m*, 5 H).

Following the above procedure, **15b**, **c**, and **f** were synthesized. With the same method but using ethyl (diethoxyphosphoryl)acetate, the (*E*/*Z*)-mixtures **15d**, **e**, and **g** were prepared. The (*E*/*Z*)-mixtures **15b–d** and **15g** were separated as above by MPLC; an attempt to separate the (*E*/*Z*)-mixtures **15e** and **15f** was unsuccessful.

*Methyl (10-Methoxy-7-methyl-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiopen-4-ylidene)acetate* (**15b**): *Isomer* (*Z*)-**15b** (47%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.35 (*s*, 3 H); 3.62 (*s*, 3 H); 3.85 (*s*, 3 H); 5.88 (*s*, 1 H); 6.09 (*s*, 1 H); 6.9–7.5 (*m*, 5 H). *Isomer* (E)-**15b** (33%): ^{1}H-NMR (80 MHz, $CDCl_3$): 2.35 (*s*, 3 H); 3.58 (*s*, 3 H); 3.83 (*s*, 3 H); 5.92 (*s*, 1 H); 6.15 (*s*, 1 H); 6.9–7.5 (*m*, 5 H).

*Methyl (7-Chloro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)acetate* (**15c**): *Isomer* (Z)-**15c** (33%): ^{1}H-NMR (200 MHz, $CDCl_3$): 3.63 (*s*, 3 H); 3.88 (*s*, 3 H); 5.87 (*s*, 1 H); 6.02 (*s*, 1 H); 7.0–7.4 (*m*, 5 H). *Isomer* (E)-**15c** (36%): ^{1}H-NMR (200 MHz, $CDCl_3$): 3.60 (*s*, 3 H); 3.88 (*s*, 3 H); 5.96 (*s*, 1 H); 6.10 (*s*, 1 H); 7.08 (*d*, *J* = 5.0, 1 H); 7.15–7.35 (*m*, 3 H); 7.39 (*d*, *J* = 5.0, 1 H).

*Ethyl (6-Chloro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)acetate* (**15d**): *Isomer* (Z)-**15d** (35%): ^{1}H-NMR (360 MHz, $CDCl_3$): 1.21 (*t*, *J* = 7.0, 3 H); 3.89 (*s*, 3 H); 4.12 (*q*, *J* = 7.0, 2 H); 5.91 (*s*, 1 H); 6.09 (*s*, 1 H); 7.07 (*d*, *J* = 5.0, 1 H); 7.2–7.3 (*m*, 2 H); 7.36 (*d*, *J* = 5.0, 1 H); 7.44 (*d*, *J* = 2.0, 1 H). *Isomer* (E)-**15d** (14%): ^{1}H-NMR (360 MHz, $CDCl_3$): 1.13 (*t*, *J* = 7.0, 3 H); 3.89 (*s*, 3 H); 4.0–4.15 (*m*, 2 H); 5.97 (*s*, 1 H); 6.16 (*s*, 1 H); 7.10 (*d*, *J* = 5.0, 1 H); 7.2–7.35 (*m*, 3 H); 7.41 (*d*, *J* = 5.0, 1 H).

*Ethyl (7-Fluoro-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ylidene)acetate* ((*E*/*Z*)-**15e**; 54%): ^{1}H-NMR (80 MHz, $CDCl_3$): 1.0–1.4 (2*t*, *J* = 7.0, 3 H); 3.7–4.4 (*m*, 5 H); 5.8–6.2 (4*s*, 2 H); 6.7–7.5 (*m*, 5 H).

Methyl (6-Fluoro-10-methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)acetate ((*E*/*Z*)-**15f**; 71%): ^{1}H-NMR (80 MHz, $CDCl_3$): 3.55–3.65 (2*s*, 3 H); 3.83 (*s*, 3 H); 5.8–6.2 (4*s*, 2 H); 6.8–7.5 (*m*, 5 H).

Ethyl (7,10-Dimethoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)acetate (**15g**): *Isomer (Z)*-**15g** (42%): ^{1}H-NMR (80 MHz, $CDCl_3$): 1.17 (*t*, *J* = 7.0, 3 H); 3.79 (*s*, 3 H); 3.86 (*s*, 3 H); 4.08 (*q*, *J* = 7.0, 2 H); 5.85 (*s*, 1 H); 6.06 (*s*, 1 H); 6.7–7.5 (*m*, 5 H). *Isomer (E)*-**15g** (28%): ^{1}H-NMR (80 MHz, $CDCl_3$): 1.14 (*t*, *J* = 7.0, 3 H); 3.81 (*s*, 3 H); 3.85 (*s*, 3 H); 4.06 (*q*, *J* = 7.0, 2 H); 5.89 (*s*, 1 H); 6.14 (*s*, 1 H); 6.7–7.5 (*m*, 5 H).

(Z)-(10-Methoxy-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)acetic Acid ((*Z*)-**8a**). To 2N NaOH/EtOH 1:2 (60 ml), (*Z*)-**15a** (4 g 0.013 mol) was added and refluxed for 4 h. EtOH was evaporated and the aq. residue diluted with H_2O. The clear soln. was acidified with 4N HCl to pH 2, whereby (*Z*)-**8a** precipitated as a yellow solid. It was filtered off, washed well with H_2O, and dried at 80° under vacuum: 2.6 g (71%). M.p. 184–187°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.90 (*s*, 3 H); 5.91 (*s*, 1 H); 6.17 (*s*, 1 H); 7.09 (*d*, *J* = 5.0, 1 H); 7.2–7.6 (*m*, 4 H); 9.7 (br., 1 H).

Following the above method, (*E*)- and (*Z*)-**8a–d**, **g** and (*E*/*Z*)-**8e**, **f** were synthesized. The mixture (*E*/*Z*)-**8f** could be separated by recrystallization from MeOH.

Isomer (E)-**8a** (76%): M.p. 168–171°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.89 (*s*, 3 H); 5.95 (*s*, 1 H); 6.23 (*s*, 1 H); 7.12 (*d*, *J* = 5.0, 1 H); 7.2–7.45 (*m*, 4 H); 11.4 (br., 1 H).

Isomer (Z)-**8b** (99%): M.p. 115–118°. ^{1}H-NMR (360 MHz, $CDCl_3$): 2.37 (*s*, 3 H); 3.90 (*s*, 3 H); 5.89 (*s*, 1 H); 6.12 (*s*, 1 H); 7.07 (*d*, *J* = 5.0, 1 H); 7.1–7.2 (*m*, 2 H); 7.29 (*d*, *J* = 5.0, 1 H); 7.36 (*d*, *J* = 8.0, 1 H). *Isomer (E)*-**8b** (97%): M.p. 177–180°. ^{1}H-NMR (360 MHz, $CDCl_3$): 2.36 (*s*, 3 H); 3.88 (*s*, 3 H); 5.93 (*s*, 1 H); 6.18 (*s*, 1 H); 7.0–7.4 (*m*, 5 H).

Isomer (Z)-**8c** (78%): M.p. 188–194°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.86 (*s*, 3 H); 5.85 (*s*, 1 H); 6.02 (*s*, 1 H); 7.01 (*d*, *J* = 5.0, 1 H); 7.2–7.4 (*m*, 4 H). *Isomer (E)*-**8c** (70%): M.p. 175–182°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.97 (*s*, 1 H); 6.10 (*s*, 1 H); 7.10 (*d*, *J* = 5.0, 1 H); 7.14–7.45 (*m*, 4 H).

Isomer (Z)-**8d** (91%): M.p. 190–191°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.91 (*s*, 1 H); 6.09 (*s*,1 H); 7.03 (*d*, *J* = 5.0, 1 H); 7.2–7.5 (*m*, 4 H). *Isomer (E)*-**8d** (87%): M.p. 206–209°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.98 (*s*, 1 H); 6.16 (*s*, 1 H); 7.11 (*d*, *J* = 5.0, 1 H); 7.2–7.5 (*m*, 4 H).

Mixture (E/Z)-**8e** (84%): M.p. 165–178°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.87–6.12 (4*s*, 2 H); 6.8–7.5 (*m*, 5 H).

Isomer (Z)-**8f** (29%): M.p. 185–190°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.91 (*s*, 1 H); 6.11 (*s*, 1 H); 7.0–7.35 (*m*, 5 H). *Isomer (E)*-**8f** (24%): M.p. 203–205°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 5.98 (*s*, 1 H); 6.17 (*s*, 1 H); 6.95–7.45 (*m*, 5 H).

Isomer (Z)-**8g** (83%): M.p. 158–168°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.84 (*s*, 3 H); 3.89 (*s*, 3 H); 5.87 (*s*, 1 H); 6.10 (*s*, 1 H); 6.75–6.95 (*m*, 2 H); 7.08 (*d*, *J* = 5.0, 1 H); 7.31 (*d*, *J* = 5.0, 1 H); 7.41 (*d*, *J* = 8.0, 1 H). *Isomer (E)*-**8g** (71%): M.p. 169–177°. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.85 (*s*, 3 H); 3.90 (*s*, 3 H); 5.93 (*s*, 1 H); 6.17 (*s*, 1 H); 6.75–6.85 (*m*, 2 H); 7.12 (*d*, *J* = 5.0, 1 H); 7.30 (*d*, *J* = 8.0, 1 H); 7.39 (*d*, *J* = 5.0, 1 H).

Biological Assays. a) *Adjuvants Arthritis.* Complete adjuvant (*F.A.*: 6 mg *Mycobacterium smegmatis S 1043* per ml mineral oil, homogenized with an *Ultraturrax*) was injected intracutaneously at the base of the tail of *Wistar* rats. Under these conditions, a primary swelling developed at the injection site and a secondary swelling in the joints of both feets, 12 to 15 days after injection. The test compounds were given orally after development of the disease (*i.e.* from day 14 to 21). Paw diameters were measured at the beginning and at the end of the treatment under light EtO anaesthesia. The body weight was determined every second day. Five animals with initial weights of *ca.* 150 g were used for each dosage. The values obtained in the treated animals are expressed as % of the control values obtained in untreated animals. ED_{50} is the dose (in mg/kg *p.o.*) causing a 50% inhibition of the induced secondary swelling.

b) *Assay for Cyclooxygenase Inhibition.* Bovine seminal vesicle microsomes suspended in 0.1M sodium phosphate buffer, containing 1 mM reduced glutathione, were incubated in the presence or absence of test substance with [^{14}C]arachidonic acid for 30 min at 37°. The reaction was terminated by acidification to pH 4. Products and unreacted substrate were extracted into AcOEt and separated by TLC and PGE_2 and $PGF_{2\alpha}$ measured radiometrically. Results are expressed as % inhibition of PGE_2 and $PGF_{2\alpha}$ synthesis in the presence of the compound under test relative to controls. IC_{50} is the concentration (in μM) causing 50% decrease in enzyme activity.

c) *Ulcerogenic Activity.* Groups of 5 or 10 rats were housed under normal conditions and given free access to food and water. Drugs were applied once daily by stomach tube for 5 consecutive days. Six h after the last dose, the rats were killed with Et_2O and the stomachs removed and opened along the greater curvature under running water and inspected for mucosal lesions. The number of rats with ulcers are expressed as a fraction of the total number of rats in the experiment. UD_{50} is the dose (in mg/kg *p.o.*) causing ulcers in 50% of the animals.

The autors would like to thank Mrs. *M. Ponelle*, Mrs. *T. Zardin*, Mr. *H. R. Loosli*, and Mr. *L. Oberer* for the NMR studies and Mrs. *S. Breiholtz*, Mr. *F. Schuerch*, and Mr. *V. Snoxall* for excellent assistance in the laboratory.

REFERENCES

[1] W. N. Kelley, E. D. Harris, R. Shaun, C. B. Sledge, 'Textbook of Rheumatology', Saunders, London, 1981.
[2] G. Kuschinsky, 'Taschenbuch der modernen Arzneimittelbehandlung', Thieme-Verlag, Stuttgart, 1980.
[3] J. D. O'Duffy, H. S. Luthra, *Drugs* **1984,** *27,* 373.
[4] J. P. Dunn, D. M. Green, P. H. Nelson, W. H. Rooks II, A. Tomolonis, K. G. Untch, *J. Med. Chem.* **1977,** *20,* 1557.
[5] K. Ueno, S. Kubo, H. Tagawa, T. Yoshioka, W. Tsukada, M. Tsubokawa, H. Kojima, A. Kasahara, *J. Med. Chem.* **1976,** *19,* 941.
[6] J. Ackrell, Y. Antonio, F. Franco, R. Landeros, A. Leon, J. M. Muchowski, M. L. Maddox, P. H. Nelson, W. H. Rooks, A. P. Roszkowski, M. B. Wallach, *J. Med. Chem.* **1978,** *21,* 1035.
[7] J. P. Dunn, J. M. Muchowski, P. H. Nelson, *J. Med. Chem.* **1981,** *24,* 1097.
[8] R. A. Appleton, K. Brown, *Prostaglandins* **1979,** *18,* 29.
[9] P. Gund, T. Y. Shen, *J. Med. Chem.* **1977,** *20,* 1146.
[10] M. Strasser, P. Cooper, B. Dewald, T. Payne, *Helv. Chim. Acta* **1988,** *71,* 1156.
[11] T. J. Carty, A. Marfat, H. Masamune, *Annual Rep. Med. Chem.* **1988,** *23,* 181.
[12] T. Y. Shen, 'Handbook of Experimental Pharmacology 1979', Springer-Verlag, Berlin, Vol. 50 (II), p. 305.
[13] J. M. Bastian, A. Ebnoether, E. Jucker, E. Rissi, A. P. Stoll, *Helv. Chim. Acta* **1965,** *49,* 214.
[14] E. Waldvogel, G. Schwarb, J. M. Bastian, J. P. Bourquin, *Helv. Chim. Acta* **1976,** *59,* 866.
[15] G. M. Davies, P. S. Davies, *Tetrahedron Lett.* **1972,** 3507.
[16] D. W. Knight, A. P. Nott, *J. Chem. Soc., Perkin Trans. 1* **1983,** 791.
[17] C. M. Pearson, *Proc. Soc. Exp. Biol. Med.* **1956,** *91,* 95
[18] M. E. J. Billingham, *Pharmac. Ther.* **1983,** *21,* 389.
[19] M. J. Seibel, W. Brueckle, M. Respondek, T. Beveridge, J. Schnyder, W. Mueller, *Z. Rheumatol.* **1989,** *48,* 147.
[20] J. Schnyder, T. G. Payne, P. Bollinger, *Agents Actions,* in press.
[21] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.