was purified with use of a column (2 × 45 cm) and solvent system C. The resulting solid was recrystallized from EtOH–Et_2O (4.1 g, 77%): mp 123–125 °C; $[\alpha]^{22}_D$ +9.9 (c 1.0, DMF). Amino acid analysis: Tyr 0.99; Met 0.97; Phe 1.00; Sar 1.01. Anal. ($C_{41}H_{57}N_5O_7S$) C, H, N.

Boc-Tyr-D-MetO-Phe-Sar-NH-Ad (13) was prepared from 12 as described for 5: mp 135–137 °C; $[\alpha]^{24}_D$ +10.1 (c 1.0, DMF). Anal. ($C_{41}H_{57}N_5O_8S$) C, H, N, S.

Preparations of Free Tetrapeptides I–IV and VI–VIII. Each Boc-protected tetrapeptide was deprotected according to procedure C. The resulting free compound (1 mmol) was dissolved in 0.5 N acetic acid (3 mL) and passed through a 2 × 50 cm Sephadex G-25 column, with solvent system A. The tetrapeptide trifluoroacetates were converted into the corresponding acetates through anion-exchange resin DE52 Whatman (acetate form) with use of 0.2 N acetic acid as eluting solvent. The fractions containing the peptide were collected and lysophilized to constant weight (85–90%). The analogues VII and VIII were obtained as free bases. Characterization of the final products are summarized in Table I.

Synthesis of Guanidino-tetrapeptide Acetate·H_2N-C-(NH)-Tyr-D-MetO-Phe-Gly-D-NH-CH(CH_3)C_6H_5 (V). The title compound was prepared by amidination of IV (1 mmol) with 1-amidino-3,5-dimethylpyrazole acetate (1.2 mmol) as in ref 7a. The crude V was reprecipitated from EtOH–AcOEt and purified by column chromatography on silica gel (2 × 60 cm) in the solvent system G. The fractions containing the pure compound were evaporated to dryness, and the residue was crystallized from AcOH–Et_2O (51%). Chracterization of V is summarized in Table I.

Pharmacological Assays. All tetrapeptides and reference compounds were assayed on electrically stimulated guinea pig ileum (GPI) with use of the conditions of Kosterlitz and Watt.[15] Dose–response curves were drawn on at least three ponts and the IC_{50}, i.e., the concentration of compound necessary to inhibit the amplitude of electrically induced twitch by 50%, was determined. Naloxone (1.4 nmol/L, i.e., the pA_2 value against dermorphin) was a potent antagonist of peptides tested at IC_{50} concentration. The analgesic potency of tetrapeptides was estimated in Swiss–Webster mice weighing 23–25 g. The tail-flick test was essentially that described by Janssen,[16] using water at 55 °C as nociceptive stimulus. Tests were made prior to and at various times after icv and sc administration of each compound in saline (4 μL). The average reaction time in control animals was 1 s. Complete analgesia was assumed to be present when no reaction appeared 10 s after application of noxious stimulus. Percent analgesia was calculated according to the formula $(T - T_0/10 - T_0) \times 100$ (T = reaction time (seconds) after administration of compound; T_0 = "normal" reaction time before injection of compound; 10 = cut off time). The specificity of the effects was tested by pretreating the animals with naloxone hydrochloride (0.5–1 mg/kg sc). In all cases, the antagonist prevented any analgesic effect.

Acknowledgment. We express our appreciation to L. Minozzi for skillful technical assistance and to Prof. F. D'Angeli and Prof. C. Bianchi for their comments and suggestions and for reading the manuscript. This research was supported by the Italian C.N.R. grant and in part by the Ministry of Public Education: Research project "Chimica, Struttura e Funzione di Peptidi".

Registry No. 1, 25616-33-5; **2a**, 42726-70-5; **2b**, 100571-96-8; **2c**, 100571-97-9; **2d**, 89661-89-2; **3a**, 100571-98-0; **3b**, 100571-99-1; **3c**, 100572-00-7; **3d**, 100572-01-8; **4a**, 100572-02-9; **4b**, 100572-03-0; **4c**, 100572-04-1; **4d**, 100572-05-2; **5a** (*R*-sulfoxide), 100572-06-3; **5a** (*S*-sulfoxide), 100679-98-9; **5b** (*R*-sulfoxide), 100572-07-4; **5b** (*S*-sulfoxide), 100679-99-0; **5c** (*R*-sulfoxide), 100572-08-5; **5c** (*S*-sulfoxide), 100680-00-0; **5d** (*R*-sulfoxide), 100572-09-6; **5d** (*S*-sulfoxide), 100680-01-1; **6**, 87976-65-6; **7**, 100572-10-9; **8**, 100572-11-0; **9** (*R*-sulfoxide), 100572-12-1; **9** (*S*-sulfoxide), 100680-02-2; **10**, 99909-57-6; 11, 100572-13-2; **12**, 100572-14-3; **13** (*R*-sulfoxide), 100572-15-4; **13** (*S*-sulfoxide), 100680-03-3; I, 100572-16-5; I·$C_2H_4O_2$, 100572-17-6; II, 100572-18-7; II·$C_2H_4O_2$, 100572-19-8; III, 100572-20-1; III·$C_2H_4O_2$, 100680-04-4; IV, 100572-21-2; IV·$C_2H_4O_2$, 100572-22-3; V, 100572-23-4; V·$C_2H_4O_2$, 100680-05-5; VI, 100572-24-5; VI·$C_2H_4O_2$, 100572-25-6; VII, 100572-26-7; VIII, 87619-62-3; I′, 78700-75-1; II′, 83579-03-7; III′, 83603-32-1; IV′, 83579-08-2; V′, 100572-27-8; VI′, 94849-58-8; Boc-Phe-Gly-OBzl, 42280-29-5; Boc-D-Met-OH, 5241-66-7; Boc-Tyr-OSu, 20866-56-2; H-D-Met-Phe-Gly-NH-CH_2-C_6H_5, 100572-28-9; H-D-Met-Phe-Gly-D-NH-CH(CH_3)C_6H_5·trifluoroacetate, 100572-30-3; H-D-Met-Phe-Gly-NH-Ad·trifluoroacetate, 100572-32-5; Boc-Phe-OSu, 3674-06-4; H-D-Met-Phe-Gly-ol·trifluoroacetate, 100572-34-7; H-Phe-OMe, 2577-90-4; H-D-Met-Phe-Gly-NH_2·trifluoroacetate, 100572-38-1; H-D-Met-Phe-OMe·trifluoroacetate, 100572-36-9; Boc-Tyr-D-Met-Phe-OH, 100572-39-2; H-Sar-NH-Ad, 100572-40-5; benzylamine, 100-46-9; (*R*)-(+)-α-methylbenzylamine, 3886-69-9; 1-adamantanamine, 768-94-5; ethanolamine, 141-43-5.

7-Aroyl-2,3-dihydrobenzo[*b*]furan-3-carboxylic Acids and 7-Benzoyl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic Acids as Analgesic Agents

Elizabeth A. Boyle, Frank R. Mangan, Roger E. Markwell,* Stephen A. Smith, Michael J. Thomson, Robert W. Ward, and Paul A. Wyman

Beecham Pharmaceuticals Research Division, Medicinal Research Centre, The Pinnacles, Harlow, Essex CM19 5AD, England.
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The synthesis of a series of 7-aroyl-2,3-dihydrobenzo[*b*]furan-3-carboxylic acids and 7-benzoyl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acids is described. The isomeric 4-benzoyl-1,3-dihydrobenzo[c]furan-1-carboxylic acid was also prepared. Compounds were evaluated for analgesic activity in the mouse phenyl-*p*-quinone-induced writhing test. Selected compounds were tested for their ability to produce gastric damage in fasted mice and for inhibition of prostaglandin synthetase activity in vitro. Zomepirac was used as a reference. Structure–activity relationships are discussed. One of the compounds, 7-benzoyl-5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylic acid (**2c**), combined potent analgesic activity with low gastric irritancy.

Gastrointestinal symptoms including mucosal damage, bleeding, and ulceration are the most common side effects of peripherally acting analgesic agents that inhibit prostaglandin synthetase.[1] One of the aims of our research program has been to identify compounds that combine the analgesic potency of zomepirac[2] (1) with a high level of gastric tolerance. In this paper we describe the synthesis and pharmacology of a series of 5-substituted 7-aroyl-

(1) Rainsford, K. D. *Agents Actions* **1977**, *Suppl. 1*, 59.

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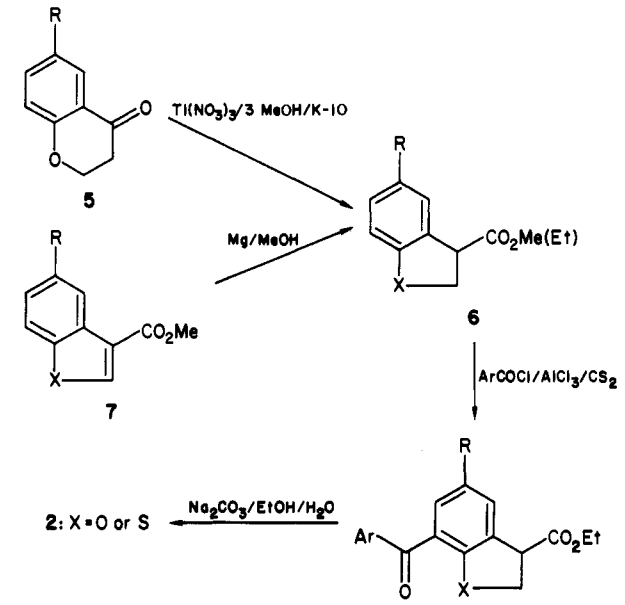
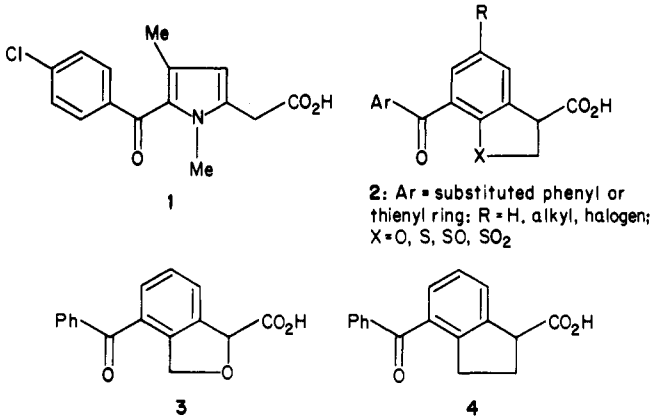
Scheme I



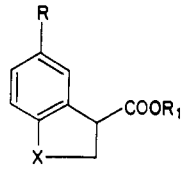
2,3-dihydrobenzo[*b*]furan- and 7-benzoyl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acids **2**, together with the isomeric 4-benzoyl-1,3-dihydrobenzo[*c*]furan-1-carboxylic acid (**3**). These compounds are related in structure to the potent analgesic, but rather ulcerogenic benzoylindanecarboxylic acid (TAI-901)[3] (**4**).



Chemistry

The synthetic procedures used for the preparation of carboxylic acids **2** are summarized in Scheme I. Rearrangement of the readily available[4] chromanones **5** by thallium trinitrate–methanol supported on K-10 clay[5,6] provided, in low yield, the intermediate 2,3-dihydrobenzo[*b*]furan-3-carboxylic esters (**6a–c**) shown in Table I (method A). An alternative high-yielding synthesis of 2,3-dihydrobenzo[*b*]furan- and 2,3-dihydrobenzo[*b*]thiophene-3-carboxylic esters was subsequently discovered[7] and used for the preparation of the remaining intermediates (**6d–g**). This method involved reduction of benzo[*b*]furan- and benzo[*b*]thiophenecarboxylic esters **7** with magnesium in methanol (method B). Conjugated olefinic

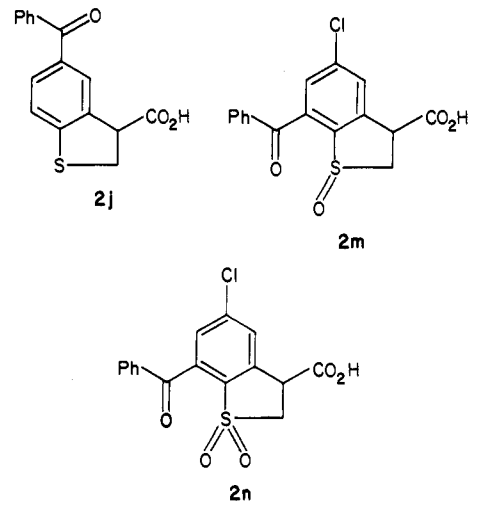
Table I. 2,3-Dihydrobenzo[*b*]furan- and -benzo[*b*]thiophene-3-carboxylic Ester Intermediates



no.	X	R	R_1	method	yield, %	formula	anal.[a]
6a	O	F	Et	A	14	$C_{11}H_{11}FO_3$	C, H
6b	O	Br	Et	A	13	$C_{11}H_{11}BrO_3$	C, H, Br
6c	O	Cl	Et	A	15	$C_{11}H_{11}ClO_3$	C, H, Cl
6d	O	Cl	Me	B	99	$C_{10}H_9ClO_3$	C, H, Cl
6e	O	Me	Me	B	92	$C_{11}H_{12}O_3$	C, H
6f	S	Cl	Et	b	83	$C_{11}H_{11}ClO_2S$	C, H, Cl
6g	S	Br	Et	c	63	$C_{11}H_{11}BrO_2S$	C, H, Br

[a] All compounds were oils and analyzed for C, H, Cl, and Br within ±0.4% of the theoretical values. [b] Reduction product was transesterified by stirring with sodium ethoxide in ethanol. [c] See the Experimental Section.

systems have previously been reduced in high yield with this reagent.[8,9] Friedel–Crafts aroylation, followed by base hydrolysis (method C), provided the 7-aroyl-2,3-dihydrobenzo[*b*]furan- and 7-benzoyl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acids **2** shown in Table II. Higher yields of product from the Friedel–Crafts reaction were isolated with ethyl rather than methyl esters **6** (compare the yield of **2c** from **6c** and **6d**), and for this reason methyl ester intermediates were usually transesterified to the ethyl esters prior to Friedel–Crafts reaction. The 5-benzoyl isomer **2j** was isolated as the major product from the



Friedel–Crafts benzoylation of the 5-bromo intermediate **6g**. Compounds lacking a 5-substituent (**2a**, **2i**) were prepared from the 5-bromo-3-carboxylic esters by hydrogenolysis over palladium on carbon, followed by base hydrolysis (method D). The sulfoxide **2m** and sulfone **2n** were prepared from the ethyl ester of **2k** by oxidation with sodium periodate and 3-chloroperbenzoic acid, respectively, followed by base hydrolysis.

The isomeric 4-benzoyl-1,3-dihydrobenzo[c]furan-1-carboxylic acid (**3**) was prepared as shown in Scheme II. Bromination of 2,3-dimethylbenzophenone with *N*-bromosuccinimide gave the unstable tribromide **8** that was immediately hydrolyzed to the aldehyde **9**. Trimethylsilyl cyanide effected the formation of the protected cyanohydrin derivative **10**, and the synthesis was completed by

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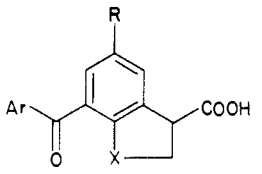
Table II. 7-Aroyl-2,3-dihydrobenzo[b]furan- and -benzo[b]thiophene-3-carboxylic Acids and Related Analogues

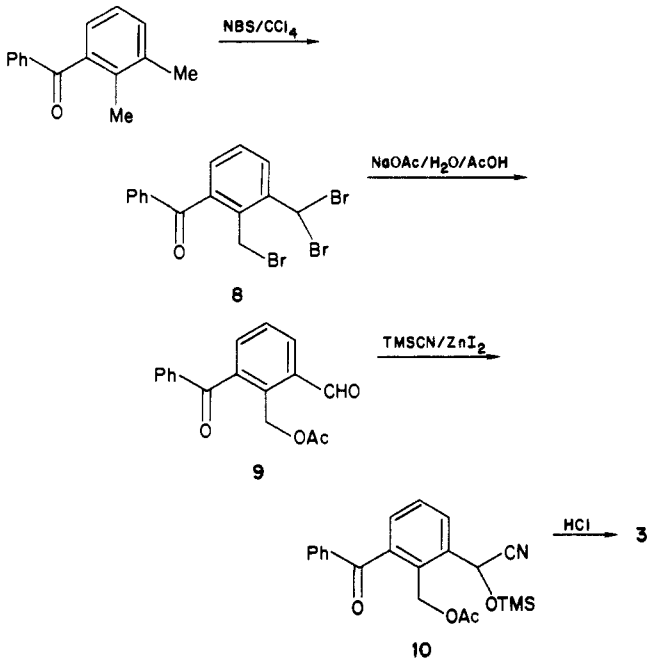


2

no.	X	R	Ar	method	yield, %	cryst solvent	mp, °C	formula	anal.[a]
2a	O	H	C_6H_5	D	33	Et_2O–pentane	166–168	$C_{16}H_{12}O_4$	C, H
2b	O	F	C_6H_5	C	6	CCl_4	135–137	$C_{16}H_{11}FO_4$	C, H
2c	O	Cl	C_6H_5	C	34 from 6c; 12 from 6d	CCl_4	155–157	$C_{16}H_{11}ClO_4$	C, H, Cl
2d	methyl ester of 2c			b	10	Et_2O–pentane	113–115	$C_{17}H_{13}ClO_4$	C, H, Cl
2e	O	Br	C_6H_5	C	35	Et_2O–pentane	173–175	$C_{16}H_{11}BrO_4$	C, H
2f	O	Me	C_6H_5	C	38[c]	Et_2O–pentane	161–163	$C_{17}H_{14}O_4$	C, H
2g	O	Cl	4′-ClC_6H_4	C	27	Et_2O–pentane	161–163	$C_{16}H_{10}Cl_2O_4$	C, H
2h	O	Cl	2′-thienyl	C	8	Et_2O–pentane	130–132	$C_{14}H_9ClO_4S$	C, H, Cl
2i	S	H	C_6H_5	D	7	Et_2O–pentane	153–156	$C_{16}H_{12}O_3S$	C, H
2j	5-benzoyl isomer of 2i			d	10	Et_2O–pentane	127–129	$C_{16}H_{12}O_3S$	C, H
2k	S	Cl	C_6H_5	C	39	Et_2O–pentane	177–179	$C_{16}H_{11}ClO_3S$	C, H, Cl
2l	S	Br	C_6H_5	C	10	Et_2O–pentane	192–194	$C_{16}H_{11}BrO_3S$	C, H
2m	SO	Cl	C_6H_5	e	14	$CHCl_3$–pentane	172–174	$C_{16}H_{11}ClO_4S$	H, Cl; C[f]
2n	SO_2	Cl	C_6H_5	e	14	Et_2O–pentane	158–161	$C_{16}H_{11}ClO_5S$	C, H
3	dihydrobenzo[c]furan			e	20	Et_2O	182–184	$C_{16}H_{12}O_4$	C, H

[a] Analysis for C, H, and Cl were within ±0.4% of the theoretical values, except as indicated. [b] Ester prepared by heating acid 2c in methanol–concentrated HCl. [c] Reaction time of only 1.5 h required. [d] Compound isolated as byproduct during preparation of 2i. [e] See the Experimental Section. [f] C: calcd, 57.40; found, 56.57.

Scheme II



hydrolysis and cyclization in hydrochloric acid.

Results and Discussion

Compounds were tested orally for analgesic activity by using the phenylquinone induced writhing test in mice. Compounds of interest were tested for their ability to inhibit prostaglandin synthetase obtained from bovine seminal vesicles. Selected compounds were also tested orally for their ability to induce gastric lesions in fasted mice. The results, together with those for zomepirac, are shown in Table III.

The 7-benzoyl-dihydrobenzo[b]furans (**2a**, **2b**, **2c**, **2f**) and dihydrobenzo[b]thiophenes (**2i**, **2k**, **2l**) showed potent analgesic activity in vivo. The effect on activity of substituents at position-5 varied between the series. In the dihydrobenzo[b]furan series, compounds with chloro and methyl substituents (**2c**, **2f**) were more potent than the corresponding unsubstituted compound **2a**. In the dihydrobenzo[b]thiophene series the 5-chloro analogue **2k** was approximately equipotent with its parent **2i**. The effect of a bromo substituent (**2e**, **2l**) was to reduce potency in both series. Replacement of the benzoyl group of **2c** by 4-chlorobenzoyl or 2-thienoyl (compounds **2g** and **2h**) resulted in reduction in activity. The methyl ester of **2c** (compound **2d**) was also of low potency. The dihydrobenzo[b]thiophene acid **2j** with the benzoyl group transposed to position-5 was less active than its isomer **2i**. A similar result has been described[10] in the indan-1-carboxylic acid series, where the 6-benzoyl isomer of

Table III. Pharmacology Data

compd	analgesic[a,b] ED_{50}[e] mg/kg po	PG[c] ID_{50}[f] μg/mL	gastric irritancy[b,d] ED_{50}[e] mg/kg po
2a	2.8 (1.5–5.3)	0.7	
2b	2.9 (1.5–5.4)		
2c	0.8 (0.5–1.3)	0.25	150 (87.2–258.0)
2d	13 (8.7–19.5)		
2e	>5		
2f	1.9 (1.1–3.2)	2	
2g	>4		
2h	>4		
2i	0.6 (0.4–0.8)	1.2	13 (7.4–24.1)
2j	>10		
2k	0.8 (0.5–1.1)	0.8	23 (10.7–51.0)
2l	1.3 (0.8–2.0)	1.4	
2m	>5	>50	
2n	>5	>50	
3	>16	5	
zomepirac	0.6 (0.4–1.0)	0.6	8 (4.2–15.4)

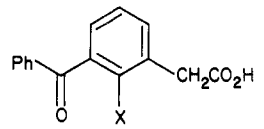
[a] Phenyl-p-quinone-induced writhing test in mice (10 mice per group). [b] 95% confidence limits described in parentheses. [c] Prostaglandin synthetase inhibition. [d] In mice (eight animals per group). [e] Calculated from single experiments using three dose levels per compound. [f] Calculated from at least four concentrations of compound.

(10) Aono, T.; Araki, Y.; Imanishi, M.; Noguchi, S. Chem. Pharm. Bull. 1978, 26, 1153.

TAI-901 (4) is only weakly active. The most active compounds of this series (**2c**, **2i**, **2k**) had a similar analgesic potency to both zomepirac and TAI-901 (reported[3] ED_{50} 1.17 mg/kg).

The ability of compounds to inhibit prostaglandin synthetase in vitro generally paralleled analgesic potency in vivo. The 5-chloro-dihydrobenzo[*b*]furan **2c** was the most active compound in this test (potency twice that of zomepirac). Chloro substitution in the phenyl ring has previously been reported[11] to enhance inhibition of prostaglandin synthetase in a related series of compounds.

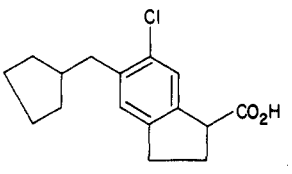
The dihydrobenzo[*c*]furan isomer of **2a** (compound **3**) and the sulfoxide **2m** and sulfone **2n** analogues of the potent dihydrobenzo[*b*]thiophene **2k** showed little activity in the analgesic test and showed reduced ability to inhibit prostaglandin synthetase in vitro compared with other members of the series. These structural modifications are expected to have little effect on steric bulk (the groups -SMe, -SOMe, and $-SO_2Me$ have similar indices of molar refraction—MR 13.82, 13.7, and 13.49, respectively[12]) but will reduce the capacity of the five-membered heterocyclic ring to donate electrons to the adjacent phenyl ring. It has been reported[13,14] previously in a related series of arylacetic acids **12** that electron-donating substituents



12: X = NH_2, OMe, Me, Cl

(NH_2, OMe, Me) at an equivalent position enhance prostaglandin synthetase inhibitory activity, whereas an electron-withdrawing group (Cl) reduces activity. Our results support the premise[13] that electronic as well as steric effects are important for binding in this type of compound.

Compounds **2c**, **2i**, and **2k** were compared with zomepirac in the gastric irritancy model and were less irritant. The low propensity of the dihydrobenzo[*b*]furan **2c** (BRL 37959) to produce gastric irritation is noteworthy, despite it being the most potent inhibitor of prostaglandin synthetase in vitro. It is structurally related to the (cyclopentylmethyl)indan **13**, which is also claimed[15] to have low ulcerogenicity. Compounds **2c** and **13** may both inhibit prostaglandin synthesis with a certain cell or tissue specificity in vivo.



13

Experimental Section

Melting points were determined with a Reichert apparatus and are uncorrected. IR, NMR, and mass spectra of all new compounds are consistent with their structures. NMR spectra were recorded either at 60 MHz on a Varian EM 360A instrument or at 270 MHz on a Jeol GX 270 instrument. Unless otherwise stated organic extracts were dried over $MgSO_4$. For column chromatography, the silica gel used was Merck Kieselgel 60. Evaporation of solvents was conducted under reduced pressure.

Method A. Ethyl 5-Chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (6c). A solution of 6-chloro-4-chromanone (21 g, 0.115 mol) in CH_2Cl_2 (100 mL) was added to a stirred suspension of thallium trinitrate (0.16 mol) absorbed on K-10 clay[5] (160 g) in CH_2Cl_2 (600 mL). The mixture was stirred at room temperature for 2.5 h and then filtered through kieselguhr. The filtrate was washed with H_2O, dried, and evaporated to leave a yellow solid, which was taken up in MeOH (100 mL), treated with 10% Na_2CO_3 (200 mL), and stirred at room temperature for 17 h. The mixture was filtered and the filtrate acidified with 5 M HCl and extracted with Et_2O. The organic solution was extracted with 5% $NaHCO_3$, which was acidified with 5 M HCl and extracted with Et_2O. The organic extract was washed with H_2O, dried, and evaporated to leave a yellow solid, which was treated with EtOH–HCl (100 mL) and heated under reflux for 1.5 h. This solution was poured into H_2O (300 mL) and extracted with Et_2O and the extract washed with H_2O, dried, and evaporated. The residue was chromatographed on a silica gel column and was eluted with 15% Et_2O–pentane to give 4.2 g (15%) of **6c** as a yellow oil: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 4.20 (q, J = 7 Hz, 2 H), 4.1–5.0 (m, 3 H), 6.68 (d, J = 8 Hz, 1 H), 7.17 (dd, J = 8 and 2 Hz, 1 H), 7.30 (d, J = 2 Hz, 1 H). Compounds **6a** and **6b** were also prepared by the procedure described above.

Method B. Methyl 5-Methyl-2,3-dihydrobenzo[*b*]furan-3-carboxylate (6e). A solution of methyl 5-methylbenzo[*b*]-furan-3-carboxylate (1.4 g 7.4 mmol) in MeOH (80 mL) was treated with magnesium turnings (890 mg, 37 mmol) and the reaction mixture stirred at room temperature, with cooling when required, until all the magnesium had reacted. The solution was poured into H_2O, acidified with 5 M HCl, and extracted with Et_2O. The organic solution was washed with H_2O, dried, and evaporated to give 1.3 g (92%) of **6e** as a pale red oil: NMR ($CDCl_3$) δ 2.22 (s, 3 H), 3.67 (s, 3 H), 4.0–5.0 (m, 3 H), 6.52 (d, J = 8 Hz, 1 H), 6.82 (dd, J = 8 and 2 Hz, 1 H), 6.97 (d, J = 2 Hz, 1 H). The preparation of compounds **6d**, **6f**, and **6g** involved the procedure described above.

Ethyl 5-Bromo-2,3-dihydrobenzo[*b*]thiophene-3-carboxylate (6g). Methyl benzo[*b*]thiophene-3-carboxylate (26.9 g, 0.14 mol) was reduced by using the procedure given in method B to give 24.6 g of methyl 2,3-dihydrobenzo[*b*]thiophene-3-carboxylate. The methyl ester (15.5 g, 0.08 mol) was transesterified by stirring at room temperature with NaOEt (0.02 mol) in EtOH (300 mL) for 1 h and then was acidified with 5 M HCl, diluted with H_2O (1.5 L), and extracted with Et_2O. The organic extract was washed with brine, dried, and evaporated to leave 15.7 g of yellow oil, which was dissolved in glacial HOAc (200 mL) and treated dropwise over 20 min with Br_2 (3.85 mL, 1 mol equiv). The solution was stirred at room temperature for 2.5 h and then diluted with H_2O (1 L) and extracted with Et_2O. The Et_2O extract was washed with aqueous Na_2CO_3, 2 M HCl, and H_2O, dried, and evaporated to leave a red oil, which was chromatographed on a silica gel column, eluting with 15% Et_2O–pentane to give 16.3 g (63% overall) of **6g** as a pale yellow oil: bp 145–150 °C (0.02 mm); NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 3.2–3.9 (m, 2 H), 4.1–4.4 (m, 1 H), 4.19 (q, J = 7 Hz, 2 H), 6.97 (d, J = 8 Hz, 1 H), 7.23 (dd, J = 8 and 2 Hz, 1 H), 7.40 (d, J = 2 Hz, 1 H).

Method C. 7-Benzoyl-5-chloro-2,3-dihydrobenzo[*b*]-furan-3-carboxylic Acid (2c). A solution of ethyl 5-chloro-2,3-dihydrobenzo[*b*]furan-3-carboxylate (**6c**) (660 mg, 2.9 mmol) in CS_2 (5 mL) was added to a stirred mixture of benzoyl chloride (2.0 mL, 17.4 mmol) and powdered $AlCl_3$ (1.94 g, 14.5 mmol) in CS_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 72 h and then poured into ice–5 M HCl and extracted with Et_2O. The organic extract was washed successively with aqueous 3-(dimethylamino)propylamine, 10% Na_2CO_3, 2 M HCl, and H_2O and then dried and evaporated to leave an orange oil. This was chromatographed on a silica gel column, eluting with 20% Et_2O–pentane to give 420 mg of the ethyl ester of **2c**, which was dissolved in EtOH (20 mL) and treated with 10% Na_2CO_3 solution (10 mL). The mixture was stirred at room temperature for 1.5 h and then acidified with 5 M HCl, concentrated to about

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half its volume, and extracted with Et_2O. The Et_2O solution was extracted with 10% Na_2CO_3 and the basic extract acidified and extracted with Et_2O. The organic solution was washed with H_2O, dried, and evaporated. The residue was crystallized from CCl_4 followed by drying under vacuum at 90 °C to give 300 mg (34%) of **2c** as a beige solid: mp 155–157 °C; NMR ($CDCl_3$) δ 4.1–5.0 (m, 3 H), 7.1–7.8 (m, 7 H), 10.13 (br s, 1 H). Compounds **2b**, **2e–h**, and **2k–l** were also prepared by using the procedure described above.

Method D. 7-Benzoyl-2,3-dihydrobenzo[*b*]furan-3-carboxylic Acid (2a). The ethyl ester of **2e** (280 mg, 0.75 mmol), prepared by method C, was dissolved in EtOAc (30 mL) and hydrogenated at room temperature and atmospheric pressure in the presence of 10% Pd–C (50 mg) and anhydrous KOAc (240 mg) for 3.5 h. The solid was removed by filtration. The filtrate was washed with H_2O, dried, and evaporated to leave a yellow oil, which was chromatographed on a silica gel column, eluting with 30% Et_2O–pentane to give 200 mg of the ethyl ester of **2a**. The ester was hydrolyzed by using the procedure given in method C to leave a colorless oil, which was crystallized from Et_2O–pentane to give 150 mg (75%) of **2a** as a white solid: mp 166–168 °C; NMR ($CDCl_3$) δ 4.1–5.0 (m, 3 H), 6.6–7.9 (m, 8 H), 7.90 (br s, 1 H). Compound **2i** was also prepared by using the procedure described above.

7-Benzoyl-5-chloro-2,3-dihydro-1-oxobenzo[*b*]thiophene-3-carboxylic Acid (2m). The ethyl ester of **2k** (346 mg, 1.0 mmol), prepared by method C, was dissolved in Me_2CO (10 mL) and treated with a solution of $NaIO_4$ (225 mg, 1.1 mmol) in H_2O (10 mL). The mixture was stirred at room temperature for 24 h and then diluted with H_2O (150 mL) and extracted with EtOAc. The organic extract was washed with H_2O, dried, and evaporated to leave a yellow oil, which was chromatographed on a silica gel column, eluting with EtOAc to give 350 mg of the ethyl ester of **2m**. The ester was hydrolyzed by using the procedure of method C and the crude acid recrystallized from $CHCl_3$–pentane to give 120 mg (36%) of **2m** as a white solid: mp 172–174 °C; NMR (CD_3OD–$CDCl_3$) δ 3.4–3.8 (m, 2 H), 3.8–4.0 and 4.9–5.1 (2 m equivalent to 1 H), 7.4–8.0 (m, 7 H).

7-Benzoyl-5-chloro-2,3-dihydro-1,1-dioxobenzo[*b*]thiophene-3-carboxylic Acid (2n). The ethyl ester of **2k** (500 mg, 1.4 mmol), prepared by method C, was dissolved in CH_2Cl_2 (30 mL), cooled in an ice bath, and treated portionwise with 3-chloroperbenzoic acid (3.1 mmol). The solution was stirred for 4 h, diluted with $CHCl_3$ (100 mL), washed with 10% Na_2CO_3, 2 M HCl, and H_2O, and then evaporated to leave a colorless oil. This was chromatographed on a silica gel column, eluting with Et_2O to give 400 mg of the ethyl ester of **2n**, which was hydrolyzed by using the procedure given in method C. The crude acid was recrystallized from Et_2O–pentane to give 220 mg (43%) of **2n** as a white solid: mp 158–161 °C; NMR ($CDCl_3$) δ 3.6–4.1 (m, 2 H), 4.4–4.7 (m, 1 H), 7.3–7.9 (m, 7 H), 8.60 (br s, 1 H).

2-[(Acetyloxy)methyl]-3-benzoylbenzaldehyde (9). Freshly recrystallized NBS (14.8 g, 0.083 mol) and dibenzoyl peroxide (50 mg) were added to a solution of 2,3-dimethylbenzophenone (8.62 g, 0.041 mol) in CCl_4 (100 mL). The mixture was heated at reflux for 2 h, cooled, and filtered. The solid was washed with CCl_4, and the combined organic solutions were evaporated, leaving a red semisolid residue (15.1 g). Freshly recrystallized NBS (3.9 g, 0.022 mol) and dibenzoyl peroxide (100 mg) were added to a solution of the above residue (8.0 g) in CCl_4 (50 mL). The mixture was heated at reflux for 16 h, cooled and filtered. The solid was washed with CCl_4, and the combined organic solutions were evaporated to give 9.0 g of crude **8**.

NaOAc (4.5 g, 0.055 mol) and H_2O (8 mL) were added to a solution of crude **8** (2.3 g, 5 mmol) in glacial HOAc (30 mL). The mixture was stirred at reflux temperature for 16 h, cooled, and diluted with Et_2O, EtOAc, and 10% Na_2CO_3. The aqueous layer was brought to pH 11 with solid Na_2CO_3, and the organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The oil (1.1 g) that remained was chromatographed on a silica gel column, eluting with 20% EtOAc–pentane to give 0.35 g (22%) of **9** as a pale yellow semisolid: NMR ($CDCl_3$) δ 1.70 (s, 3 H), 5.43 (s, 2 H), 7.1–8.2 (m, 8 H), 10.23 (s, 1 H). Anal. ($C_{17}H_{14}O_4$) C, H.

The positions of the acetoxymethyl and aldehyde groups (relative to the benzoyl function) were confirmed by high-field NMR using a nuclear Overhauser effect difference technique.

4-Benzoyl-1,3-dihydrobenzo[*c*]furan-1-carboxylic Acid (3). 2-(Acetoxymethyl)-3-benzoylbenzaldehyde (**9**) (290 mg, 1 mmol) was treated, under nitrogen, with trimethylsilyl cyanide (100 mg, 1 mmol) and ZnI_2 (20 mg). The mixture was heated at 65 °C for 0.5 h and stirred at room temperature for 16 h. Concentrated HCl (5 mL) was added, and the mixture was heated at 80 °C for 1 h. The cooled slurry was extracted with EtOAc. The organic solution was extracted with $NaHCO_3$ solution, which was acidified with 5 M HCl and extracted with EtOAc. The organic extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue was crystallized from Et_2O to give 55 mg (20%) of **3** as a pale yellow solid: mp 182–184 °C; NMR (CD_3OD) δ 5.46 (m, 2 H), 5.73 (m, 1 H), 7.4–7.9 (m, 8 H).

Pharmacology. Phenyl-*p*-quinone Writhing Test. The method of Hendershot and Forsaith[16] was employed. Male mice (10 in each group) received test compounds orally, 1 h prior to an intraperitoneal injection of 0.2 mL of phenyl-*p*-quinone solution. The animals were observed for a subsequent 8 min, and those failing to writhe within this time were considered to be showing analgesia. The ED_{50} value was calculated from dose–response lines as the dose expected to produce analgesia in 50% of the animals.

Ulcerogenic Activity. The method of Hitchens et al.[17] was used. Male mice (eight in each group) were fasted overnight and given test compounds orally. Four hours later the animals were killed, and the stomachs were removed, stretched, and examined for the presence of bleeding erosions of the mucosa. ED_{50} values were calculated from dose–response lines as the dose expected to induce observable mucosal damage in 50% of the animals.

Prostaglandin Synthetase Inhibition. A microsomal preparation capable of effecting prostaglandin synthesis from arachidonic acid was made from bovine seminal vesicles by the method of Yoshimoto et al.[18] Aliquots were incubated in vitro with [^{3}H]arachidonic acid and essential cofactors with or without test compounds. Dose-related inhibition of [^{3}H]-PGE_2 synthesis was obtained by using at least four concentrations of each compound, in duplicate. ID_{50} values were calculated from dose–response lines as the dose expected to produce 50% inhibition of prostaglandin synthesis.

Registry No. 2a, 93670-36-1; **2a** (ethyl ester), 93670-35-0; **2b**, 93669-90-0; **2c**, 93669-83-1; **2c** (ethyl ester), 93669-82-0; **2d**, 101166-62-5; **2e**, 93669-81-9; **2e** (ethyl ester), 93670-34-9; **2f**, 91503-30-9; **2g**, 93669-88-6; **2h**, 93669-86-4; **2i**, 93669-93-3; **2j**, 91503-28-5; **2k**, 93669-96-6; **2k** (ethyl ester), 93669-95-5; **2l**, 93669-94-4; **2m**, 93669-98-8; **2m** (ethyl ester), 93669-97-7; **2n**, 93670-00-9; **2n** (ethyl ester), 93669-99-9; **3**, 93669-84-2; **5** (R = F), 66892-34-0; **5** (R = Br), 49660-57-3; **5** (R = Cl), 37674-72-9; **6a**, 93670-20-3; **6b**, 93670-11-2; **6c**, 93670-13-4; **6c** (acid), 93670-12-3; **6d**, 93670-33-8; **6e**, 93670-28-1; **6f**, 93670-24-7; **6g**, 93670-21-4; **7** (X = O R = Cl), 93670-32-7; **7** (X = O R = Me), 93670-27-0; **7** (X = S R = Cl), 93670-22-5; **7** (X = S R = H), 22913-25-3; **8**, 93670-15-6; **9**, 93670-16-7; ZnI_2, 10139-47-6; methyl 2,3-dihydrobenzo[*b*]thiophenecarboxylate, 39891-63-9; ethyl 2,3-dihydrobenzo[*b*]thiophenecarboxylate, 19156-48-0; benzoyl chloride, 98-88-4; 2,3-dimethylbenzophenone, 13319-69-2; trimethylsilyl cyanide, 7677-24-9; *p*-chlorobenzoyl chloride, 122-01-0; 2-thiophenecarbonyl chloride, 5271-67-0; prostaglandin synthetase, 9055-65-6.

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