Grossman, M. I. (1956) Duration of action of antacids. Am. J. Dig. Dis. 1: 435–454

Hardy, J. G., Perkins, A. C. (1985) Validity of the geometric mean correction in the quantification of whole bowel transit. Nucl. Med. Comm. 6: 217–224

Jenkins, J. R. F., Hardy, J. G., Wilson, C. G. (1983) Monitoring antacid preparations in the stomach using gamma scintigraphy. Int. J. Pharm. 14: 143–148

Laitinen, S., Stahlberg, M., Kairaluoma, M. I., Kiviniemi, H., Paakkonen, M., Lahtinen, J., Poikolainen, E., Aukee, S. (1985) Sucralfate and alginate/antacid in reflux oesophagitis. Scand. J. Gastroenterol. 20: 229–232

May, H. A., Hardy, J. G., Wilson, C. G. (1984) Monitoring radiolabelled antacid preparations in the stomach. Int. J. Pharm. 19: 169–176

O'Reilly, S., Wilson, C. G., Hardy, J. G. (1987) The influence of food on the gastric emptying of multiparticulate dosage forms. Ibid. 34: 213–216

Washington, N., Washington, C., Wilson, C. G., Davis, S. S. (1986a) The effect of inclusion of aluminium hydroxide in alginate-containing raft-forming antacids. Ibid. 28: 139–143

Washington, N., Washington, C., Wilson, C. G., Davis, S. S. (1986b) What is Liquid Gaviscon? A comparison of four international formulations. Ibid. 34: 105–109

Washington, N., Washington, C., Wilson, C. G. (1987) Gastric distribution and residence time of two anti-reflux formulations. Ibid. 39: 163–171

J. Pharm. Pharmacol. 1990, 42: 53–55
Communicated June 20, 1989

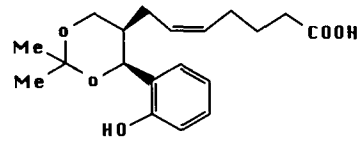
© 1990 J. Pharm. Pharmacol.

Improved synthetic routes to the novel thromboxane receptor antagonist ICI 192605: activity of synthetic 1,3-dioxane intermediates

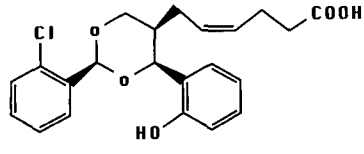
GEORGE R. BROWN, ALAN J. FOUBISTER, JULIAN A. HUDSON, *ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

Abstract—A study of the synthetic routes to the thromboxane receptor antagonist ICI 192605 4(Z)-6-(2-*o*-chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl) hexenoic acid is described which led to an improvement in overall synthetic yield from 20 to 55%. In-vitro thromboxane receptor antagonist data are reported for the novel 1,3-dioxane synthetic intermediates. These data indicated that shortening of the side chain in an appropriately substituted 2,2-dimethyl-1,3-dioxane (e.g. ICI 180080) from a heptenoic acid, to a hexenoic acid, had little effect on thromboxane receptor antagonist potency ($pA_2 = 7.5$ rabbit thoracic aorta for the heptenoic acid ICI 180080 and $pA_2 = 6.9$ for the corresponding hexenoic acid. Human platelet aggregation pA_2 values were 6.7 and 7.0, respectively).

Thromboxane A_2 is an unstable metabolite of arachidonic acid which is both a constrictor of smooth muscle and a blood platelet aggregator. These pharmacological actions may play a role in the pathology of a number of life threatening diseases (Fitzgerald et al 1988) such as angina, stroke and asthma. Blockage of the actions of thromboxane A_2 by a selective thromboxane receptor antagonist may facilitate the study of these diseases and eventually establish thromboxane receptor antagonists as novel therapeutic agents.



Structure 1



Structure 2

Correspondence to: G. R. Brown, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK.

We have previously described the original synthesis and pharmacological properties of the novel 1,3-dioxane thromboxane antagonists ICI 180080 (**1**) (Brown & Foubister 1986) and its more potent and stable analogue 4(Z)-6-(2-*o*-chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl)hexenoic acid, ICI 192605 (**2**) (Brown et al 1988). We now report an investigation of the synthetic routes to **2** aimed at improving the synthesis for the preparation of sufficient material for pharmacological and pre-development work. Included are the in-vitro thromboxane receptor antagonist activities of the novel synthetic intermediates involved.

Materials and methods

Chemistry. To prepare the desired thromboxane antagonist (**2**) from the intermediate (**3**) (Brown et al 1988) two synthetic operations are required (Fig. 1): demethylation of the methyl phenyl ether group under non-acidic conditions and replacement of the 2,2-substituted methyl groups of the 1,3-dioxane ring of **3** with an ortho-chlorophenyl ring, either by direct exchange or via a ring opened 1,3-diol such as **6**. By variation of the sequence of these steps, four different preparative routes to the dioxane (**2**) resulted (Routes A, B, C_1 and C_2, Fig. 1) and were compared.

In route A, demethylation of the methyl ether (**3**) with sodium thioethoxide to the corresponding phenol (**4**) using six molar equivalents of the thiol reagent improved the yield from 31% (Brown et al 1988) to 84%. Demethylation of **3** with diphenyllithium phosphide (Ireland & Walba 1977) resulted in the lower yield of 54%. Route A was completed by acetal exchange with 2-chlorobenzaldehyde. In route B, acetal exchange was carried out before demethylation but in the subsequent demethylation with sodium thioethoxide, lower yields of the phenol (**2**) were obtained, presumably due to some attack of the thiol reagent at the aryl chlorine atom. Cleavage of the 1,3-dioxane ring of **3** with dilute hydrochloric acid afforded the 1,3-diol (**6**) in quantitative yield. Sodium thioethoxide ether fission (Route C_1) of the diol (**6**) to give the triol (**7**) was also high yielding, but ring closure with 2-chlorobenzaldehyde gave **2** in only 43% yield. 1,3-

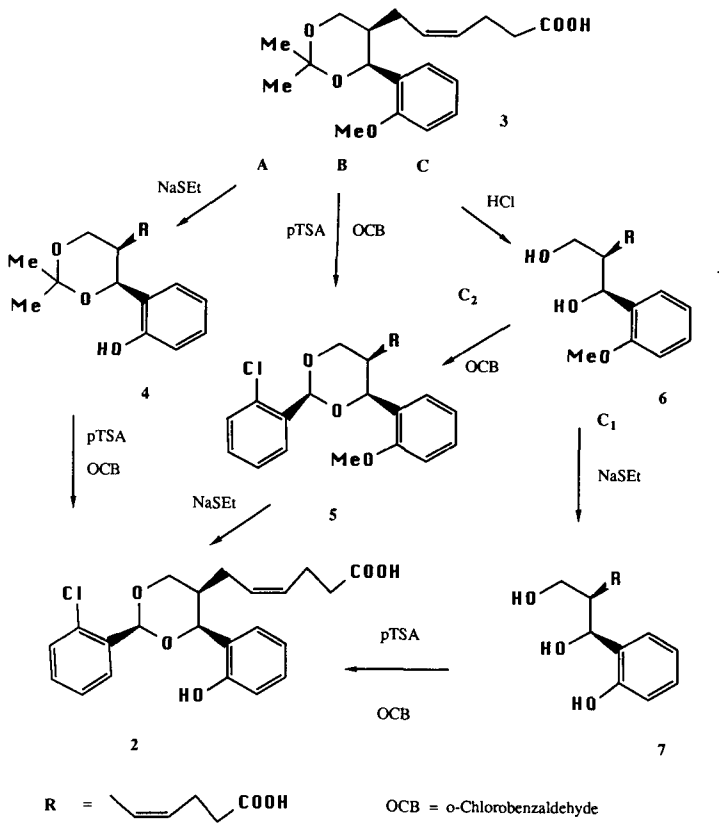


Figure 1 Synthetic routes to ICI 192605 (2)

Dioxane ring formation proceeded competitively with ring closure involving the phenolic hydroxyl group: product purification also proved difficult in this step. The final synthetic route examined (Route C_2), also gave a poor yield (39%) on ring closure with 2-chlorobenzaldehyde.

Pharmacological methods. Test compounds were initially examined for their ability to inhibit U46619 (Bundy 1975) induced contractions of isolated strips of rabbit thoracic aorta. This ability was taken as a measure of thromboxane receptor antagonism and test results were expressed as pA_2 values. Additionally venous blood was taken from volunteers into 3·2% (w/v) trisodium citrate and centrifuged at 200 *g* for 10 min. The platelet rich plasma was aggregated by U 46619, 60 s after the addition of test compound and in the absence of test compound. Results were expressed as pA_2 values. Detailed pharmacological methods have been reported (Jessup et al 1986).

Results and discussion

The overall yields for the synthetic routes examined (A, B, C_1 and C_2) were 55, 32, 40 and 16%, respectively. This shows that the two step process route A gave the highest yield of 55%. It represents a significant improvement over the originally reported yield of 20% (Brown et al 1988).

The thromboxane receptor antagonist properties in-vitro of the synthetic 1,3-dioxanes is recorded in Table 1. From these limited data the following preliminary deductions can be made. Consideration of compounds **3** and **5** indicated that substitution of the 4-aryl ring by a methoxyl group afforded little or no antagonism at the human platelet receptor. The 2-*o*-chlorophenyl substitution present in ICI 192605 (**2**) afforded an order of magnitude improvement in potency over the otherwise analogous 2,2-dimethyl substituted dioxane (**4**). Interestingly a comparison of the activity of the 1,3-dioxanes **1** and **4** suggests that merely shortening the side chain from a heptenoic acid to a hexenoic acid does not account for the order of magnitude increase found for the antagonism of dioxane **2** over dioxane **4**.

Table 1. Thromboxane receptor antagonist data.

	pA_2 vs U46619*	
Compound	Rabbit thoracic aorta	Human platelet aggregation
1	7·5	6·7
2	8·0	8·3
3	6·5	5·1
4	6·9	7·0
5	6·7	< 5·0

* (15S)-hydroxy-11α 9β-(epoxymethano) prosta-5Z,13E dienoic acid.

Preparative work. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz) instrument and mass spectra on a MS902 Kratos (AEI) spectrometer. Assigned structures were supported by elemental microanalyses and ^{1}H NMR data. Silica gel was Merck Kieselgel (Art. 9385).

4(Z)-6-(4-o-Hydroxyphenyl-2,2-dimethyl-1,3-dioxan-cis-*5-yl) hexenoic acid* (**4**). (a) Sodium hydride (3·02 g, 50% w/w dispersion in mineral oil) was added to a solution of the 1,3-dioxane (**3**) (3·5 g) in 1,3-dimethyl-3, 4, 5, 6-tetrahydro-2(1H)-pyrimidinone (DMPU) at 0–5°C. After 5 min ethanethiol (4 mL) was added during 10 min and heated to 135–140°C for 50 min.

The cooled mixture was diluted with water, washed with dichloromethane and the aqueous phase acidified to pH4 with acetic acid. Evaporation of dried ($MgSO_4$) diethyl ether extracts gave an oil which was purified by flash column chromatography on silica gel in toluene - ethyl acetate - acetic acid (80: 20: 2, by volume) to give as a colourless solid, **4** (2·8 g, 84%) m.p. 87–90°C; (Found C, 67·2; H, 7·6 C_{18} H_{24} O_5 requires C, 67·5; H, 7·6%) δ ($CDCl_3$) 1·6 (8H, s), 2·3 (3H, s), 2·7 (1H, m), 4·0 (2H, q), 5·4 (3H, m), 7·0 (4H, m) and 8·4 (2H, s) ppm. *m/z* 320 (M^+).

(b) Lithium (280 mg) was added cautiously to a solution of chlorodiphenyl phosphine (1·8 mL) in tetrahydrofuran (10 mL). After 3 h the resulting solution was added to **3** (668 mg) in tetrahydrofuran (2 mL) at 0°C. The reaction was heated at 50°C for 3 h, cooled and poured onto ice/water. The aqueous mixture was washed with dichloromethane and acidified to pH 4 with acetic acid. An ether extract was washed with brine, dried ($MgSO_4$) and evaporated to give an oil which was purified as in (a) to give **4** (330 mg, 54%) m.p. 87–90°C.

*4(Z)-6-(2-*o*-Chlorophenyl-4-*o*-hydroxyphenyl-1,3-dioxan-*cis*-5-yl) hexenoic acid* (**2**). (a) *o*-Chlorobenzaldehyde (6·8 g) and *p*-toluenesulphonic acid (100 mg) were added to a solution of **4** (13·2 g) in toluene (120 mL). The mixture was stirred for 3 h and the product isolated by chromatography on silica gel eluting with ethanol:dichloromethane (1:19, by volume) to give as a colourless solid **2** (10·8 g, 65%) m.p. 125–126°C. (Found C, 65·7; H, 5·9 C_{22} $H_{23}ClO_5$ requires C, 65·7; 5·9%) δ ($CDCl_3$) 1·82 (1H, m), 1·96 (1H, m), 2·36 (4H, m), 4·2 (2H, m), 5·41 (3H, m), 6·12 (1H, s), 6·9 (2H, m), 7·35 (5H, m) and 7·87 (1H, m) ppm *m/z* 402 (M^+).

(b) Sodium hydride (288 mg, 50% dispersion in mineral oil) was added to **5** (416 mg) in DMPU (14 mL) at 0–5°C and after 5 min ethanethiol (0·45 mL) was added. The mixture was heated at 90°C for 6 h and worked up as described for **4** above. Flash column chromatography on silica gel in toluene–ethyl acetate–acetic acid (80:20:1, by volume) gave as a colourless solid **2** (168 mg, 42%) m.p. 125–126°C.

(c) *o*-Chlorobenzaldehyde (100 mg) and *p*-toluene sulphonic acid (2 mg) were added to a solution of **7** (140 mg) in toluene (2 mL) and the mixture stirred for 20 h. The product was isolated as in (a) above to give as a colourless solid **2** (86 mg, 43%) m.p. 125–126°C.

*4(Z)-6-(2-Chlorophenyl-4-*o*-methoxyphenyl-1,3-dioxan-*cis*-5-yl) hexenoic acid* (**5**). (a) *o*-Chlorobenzaldehyde (420 mg) and *p*-toluene sulphonic acid (5 mg) were added to a solution of **3** (668 mg) in toluene (12 mL) and the mixture heated at 105°C for 30 min. The mixture was cooled and the product isolated by flash column chromatography on silica gel eluting with dichloromethane - ethanol (97:3, by volume) to give as a colourless solid **5** (625 mg, 75%) m.p. 147–150°C (Found C, 66·1, H, 6·1 C_{23} $H_{25}Cl$ O_5 requires C, 66·3; H, 6·0%) δ ($CDCl_3$) 1·72 (1H, m), 2·00 (1H, m), 2·30 (4H, m), 2·63 (1H, m), 3·85 (3H, s), 4·20 (2H, d), 5·35 (3H, m), 6·10 (1H, s) 6·91 (2H, m), 7·30 (4H, m), 7·45 (1H, d) and 7·91 (1H, m) ppm. *m/z* 416 (M^+).

(b) *o*-Chlorobenzaldehyde (52 mg) and *p*-toluene sulphonic acid (2 mg) were added to a suspension of **6** (82 mg) in toluene (1 mL) and the mixture stirred for 3 h at 25°C. The product was isolated as for (a) above to give as a colourless solid **5** (44 mg, 39%) m.p. 147–150°C.

*4(Z)-Erythro-8-hydroxy-7-hydroxymethyl-8-*o*-methoxyphenyl-4-octenoic acid* (**6**). A solution of **3** (2 g) in tetrahydrofuran (80 mL) and 2M-hydrochloric acid (2 mL) was heated at 70°C for 1 h and the tetrahydrofuran was evaporated. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate was washed with brine, dried ($MgSO_4$) and evaporated to give an oil which was purified by flash column chromatography on silica gel in hexane - ethyl acetate–acetic acid (40:60:1, by volume) to give as a colourless oil **6** (1·79 g, 100%) (Found C, 63·6; H, 7·5 $C_{16}H_{22}O_5.1/_2H_2O$ requires C, 63·3; H 7·6%) *m/z* 294 (M^+).

*4(Z)-Erythro-8-hydroxy-7-hydroxymethyl-8-*o*-hydroxyphenyl-4-octenoic acid* (**7**). Sodium hydride (980 mg, 60% w/w dispersion in mineral oil) was added to a suspension of **6** (900 mg) in DMPU (35 mL) at 0–5°C and after 5 min ethanethiol (1·5 mL) was added. The mixture was heated at 130°C for 2 h and cooled. The mixture was diluted with water and washed with dichloromethane when the aqueous phase was acidified to pH4 and extracted with diethyl ether. The ether was washed with brine, dried ($MgSO_4$) and evaporated to give an oil which was purified by flash column chromatography on silica gel in toluene - ethyl acetate - acetic acid (60: 40:2, by volume) to give as a colourless oil **7** (785 mg, 92%) (Found C, 64·5; H, 7·0 C_{15} H_{20} O_5 requires C 64·3; H 7·1% δ ($CDCl_3$) 1·83 (1H,m), 2·44 (6H, m), 3·73 (3H, m), 4·50 (2H, m), 5·32 (3H, m) and 6·99 (4H, m) ppm.*m/z* 280 (M^+).

References

Brown, G. R., Foubister, A. J. (1986) ICI 180080, a novel selective thromboxane receptor antagonist: synthesis and relative activity. J. Pharm. Pharmacol. 38: 706–708

Brown, G. R., Brewster, A. G., Foubister, A. J., Jessup, R., Smithers, M. J. (1988) The synthesis of a novel thromboxane receptor antagonist 4(Z)-6-(2-o-chlorophenyl-4-o-hydroxyphenyl-1,3-dioxan-cis-5-yl) hexenoic acid ICI 192605. Prostaglandins 36: 173–178

Bundy, G. L. (1975) The synthesis of prostaglandin endoperoxide analogs. Tetrahedron Lett. 24: 1957–1960

Fitzgerald, G. A., Branch, R. A., Jackson, E. K., Jackson Roberts, L., Knapp, H. R., Oates, J. A. (1988) Clinical implications of prostaglandin and thromboxane A_2 formation. N. Engl. J. Med. 319: 689–698 and 761–767

Ireland, R. E., Walba, D. M. (1977) Demethylation of methyl aryl ethers: 4-ethoxy-3-hydroxybenzaldehyde. Org. Syn. 56: 44–48

Jessup, C. L., Jessup, R., Wayne, M. (1986) Pharmacological actions of ICI 180080, a novel thromboxane receptor antagonist. J. Pharm. Pharmacol. 38: 754–757