Pharmacologically Active Benzo[*b*]thiophen Derivatives. Part X.[1] 2-(5- and 7-Hydroxy-3-benzo[*b*]thienyl)ethylamines and Related Compounds

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Some 2- and 3-dialkylaminomethyl-5-methoxybenzo[*b*]thiophens have been prepared from the appropriate bromomethyl compound and secondary amines. The bromomethyl compounds have been converted into the corresponding nitriles and reduced to 2-(5-methoxy-2- or -3-benzo[*b*]thienyl)ethylamine. 2-(5-Hydroxy-3-benzo[*b*]thienyl)ethylamine has been prepared from 5-nitro-3-benzo[*b*]thienylacetic acid and isolated and characterised as its maleate. The isomeric 7-hydroxy-compound has been prepared from 7-hydroxy-3-methylbenzo[*b*]-thiophen *via* the nitrile and has been isolated as its hydrochloride.

THE theory of bio-isosterism [2,3] has promoted considerable interest in the preparation of benzo[*b*]thiophen analogues of biologically active indole derivatives. The benzo[*b*]thiophen analogues of heteroauxin,[4] tryptophan,[5] and tryptamine [6] have been reported and many benzo[*b*]-thiophen compounds structurally related to gramine,[7] serotonin,[8] and harman [9] have been prepared. Because of the widespread biological action of serotonin (5-hydroxytryptamine, 5-HT), the preparation of its benzo-[*b*]thiophen analogue has received particular attention. The first syntheses [10] gave very poor yields, but Campaigne and Dinner [11] have recently described an eight-stage synthesis for which they claim an overall yield of 20% from commercially available *m*-hydroxyacetophenone. We now describe our efforts in this field, including a synthesis of the benzo[*b*]thiophen analogue of serotonin and its *O*-methyl ether and of the isomeric 2-(7-hydroxy-3-benzo[*b*]thienyl)ethylamine.

Esterification of 5-methoxybenzo[*b*]thiophen-2-carboxylic acid with hot ethanol and concentrated sulphuric acid, followed by reduction with lithium aluminium hydride, gave 2-hydroxymethyl-5-methoxybenzo[*b*]thiophen, which was readily converted into the 2-bromomethyl derivative by reaction with phosphorus tribromide. 3-Bromomethyl-5-methoxybenzo[*b*]thiophen was obtained by decarboxylation of 5-methoxy-3-methylbenzo[*b*]thiophen-2-carboxylic acid, followed by bromination of the 3-methyl group by methods previously described.[12] 2-Bromomethyl-5-methoxybenzo[*b*]thiophen was condensed with diethylamine or with pyrrolidine in boiling benzene as previously described,[12] and both the 2- and the 3-bromomethyl compound were condensed with 2-ethylaminoethanol, and the resulting 2-hydroxyethylamines reacted with thionyl chloride in boiling chloroform [13] to give the corresponding 5-methoxy-2- or -3-(*N*-2-chloroethyl-*N*-ethylaminomethyl)-benzo[*b*]thiophen hydrochloride. Reaction of the 2- or the 3-bromomethyl compound with sodium cyanide in dimethyl sulphoxide gave the corresponding cyanomethyl derivatives, each of which was reduced with lithium aluminium hydride–aluminium chloride to the corresponding ethylamine derivative.[8] Treatment of these primary amine hydrochlorides with aqueous potassium cyanate gave the corresponding urea.

Although 5-hydroxy-3-methylbenzo[*b*]thiophen is readily prepared by modification of the method of Campaigne, Bosin, and Neiss,[10] its transformation into the *S*-analogue of serotonin without some suitable protection of the hydroxy-group seemed most unlikely. We therefore used *m*-benzyloxyacetophenone in the initial condensation with rhodanine, and after hydrolysis of the rhodanine derivative, cyclisation of the resulting α-mercaptoacrylic acid with chlorine, and decarboxylation of the acid formed, we obtained an overall yield of 37% of 5-benzyloxy-3-methylbenzo[*b*]thiophen. However, attempted bromination of this compound with *N*-bromosuccinimide gave an unstable mixture of products, presumably owing to competing bromination of the benzylic methylene and the methyl group, and so this route was abandoned.

We therefore investigated methods which did not involve this bromination step. Reduction of 5-nitro-3-benzo[*b*]thienylacetic acid [14] with Raney nickel and hydrazine hydrate, followed immediately by diazotisation and boiling the solution so produced, gave 5-hydroxy-3-benzo[*b*]thienylacetic acid. This was esterified with hot methanol and sulphuric acid and the ester was treated, without purification, with an excess of concentrated ammonia to give the corresponding amide. Reduction of this amide with diborane in tetrahydrofuran gave the *S*-analogue of serotonin [2-(5-hydroxy-3-benzo[*b*]thienyl)ethylamine], which was isolated and

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characterised as its maleate. This procedure is long (eleven stages from commercially available 2-chloro-5-nitrobenzoic acid) but gives an overall yield of 7—8% and is far superior to the methods first published,[9] although less efficient than Campaigne's latest preparation.[10]

We recently described [15] a new preparation of 7-hydroxy-3-methylbenzo[*b*]thiophen, and as both Martin-Smith and Campaigne have demonstrated that the presence of an electron-withdrawing protecting group (methylsulphonyl or benzoyl) on the hydroxy-group permits the side-chain bromination of 5-hydroxy-3-methylbenzo[*b*]thiophen, we attempted the preparation of 2-(7-hydroxy-3-benzo[*b*]thienyl)ethylamine. 3-Methyl-7-methylsulphonyloxybenzo[*b*]thiophen was treated with *N*-bromosuccinimide in boiling carbon tetrachloride and the resulting 3-bromomethyl compound was converted into the 3-cyanomethyl derivative by reaction with potassium cyanide in boiling aqueous acetone. Removal of the protecting group by treatment with sodium in ethanol gave 3-cyanomethyl-7-hydroxybenzo-[*b*]thiophen (71%) and a by-product (26%), thought to be 3-cyanomethyl-7-ethoxybenzo[*b*]thiophen. Reduction of the 3-cyanomethyl-7-hydroxybenzo[*b*]thiophen with diborane in tetrahydrofuran gave 2-(7-hydroxy-3-benzo[*b*]thienyl)ethylamine, which was isolated and characterised as its hydrochloride.

EXPERIMENTAL

5-Methoxybenzo[*b*]thiophen-2-carboxylic acid and its 3-methyl derivative were prepared by published methods.[16]

Ethyl 5-methoxybenzo[b]*thiophen-2-carboxylate* (47%), prepared by boiling the corresponding acid with ethanol in the presence of concentrated sulphuric acid,[1] had b.p. 166—170° at 1·5 mmHg, m.p. 64—65° (from ethanol) (Found: C, 61·0; H, 5·0. $C_{12}H_{12}O_3S$ requires C, 61·0; H, 5·1%), $\nu_{max.}$ 1705 (C=O) cm^{-1}.

2-Hydroxymethyl-5-methoxybenzo[b]*thiophen* (77%), obtained by reduction of the corresponding ester with lithium aluminium hydride in dry ether,[17] had m.p. 124—126° (from benzene) (Found: C, 61·9; H, 5·1; S, 16·2. $C_{10}H_{10}O_2S$ requires C, 61·9; H, 5·2; S, 16·5%), $\nu_{max.}$ 3230 (OH) cm^{-1}.

2-Bromomethyl-5-methoxybenzo[b]*thiophen.*— Phosphorus tribromide (12·0 g, 0·044 mol) in dry ether (100 ml) was added to a stirred solution of 2-hydroxymethyl-5-methoxybenzo[*b*]thiophen (22·0 g, 0·103 mol) and dry pyridine (1·5 ml) in dry ether (1 l) during 20 min. The mixture was boiled for 2 h, cooled, and poured into ice–water (2 l). The aqueous layer was separated and shaken with ether (3 × 200 ml), and the combined ethereal extracts were washed with aqueous 10% sodium carbonate (3 × 200 ml) and with water (3 × 200 ml), and dried ($MgSO_4$). Evaporation gave a yellow solid which was crystallised from benzene–light petroleum (b.p. 60—80°). The *bromomethyl compound*, m.p. 98—100° (23·8 g, 89%), was unstable and was used immediately.

3-Bromomethyl-5-methoxybenzo[b]*thiophen* (59%), prepared by the reaction of 5-methoxy-3-methylbenzo[*b*]thiophen with *N*-bromosuccinimide in boiling carbon tetrachloride,[12] had m.p. 76—77° [from benzene–light petroleum (b.p. 60—80°)]. It was used immediately.

N-Substituted 2- and 3-Aminomethyl-5-methoxybenzo[b]*thiophen Hydrochlorides.*—2-Bromomethyl-5-methoxybenzo[*b*]-thiophen was condensed with diethylamine or with pyrrolidine in boiling benzene.[12] Both 2- and 3-bromomethyl-5-methoxybenzo[*b*]thiophen were condensed with 2-ethylaminoethanol in boiling benzene and the resulting *amino-alcohols* were converted into the corresponding *2-chloroethylamines* by treatment with thionyl chloride in dry, boiling chloroform.[13] Details of the products are given in the Table.

2- or 3-Cyanomethyl-5-methoxybenzo[b]*thiophen.*—Reaction of 2- or 3-bromomethyl-5-methoxybenzo[*b*]thiophen with sodium cyanide in dimethyl sulphoxide [8] gave the corresponding *nitriles*. These were reduced with lithium aluminium hydride and aluminium chloride in dry ether to *2-(5-methoxy-2- or -3-benzo*[b]*thienyl)ethylamine*. Condensation of these primary amine hydrochlorides with aqueous potassium cyanate at room temperature overnight gave the corresponding *ureas*. The yields and analytical results for these compounds are given in the Table.

5-Benzyloxy-3-methylbenzo[b]*thiophen.*— 3-Benzyloxyacetophenone was condensed with rhodanine [16] to give *5-(3-benzyloxy-α-methylbenzylidene)rhodanine* (73%), m.p. 129—131° (from ethanol) (Found: C, 63·6; H, 4·5; N, 4·2; S, 19·0%; *M*, 341. $C_{18}H_{15}NO_2S_2$ requires C, 63·3; H, 4·4; N, 4·1; S, 18·8%; *M*, 341), $\nu_{max.}$ 1690 (C=O) cm^{-1}. Hydrolysis for 30 min with hot aqueous 20% sodium hydroxide gave *β-(3-benzyloxyphenyl)-α-mercapto-β-methylacrylic acid* (80%), which was not purified but was cyclised immediately with chlorine in dry carbon tetrachloride to give *5-benzyloxy-3-methylbenzo*[b]*thiophen-2-carboxylic acid* (70%), m.p. 198—200° (from benzene) (Found: C, 68·5; H, 4·7; S, 10·9%; *M*, 298. $C_{17}H_{14}O_3S$ requires C, 68·4; H, 4·7; S, 10·7%; *M*, 298), $\nu_{max.}$ 3200—2200br (OH) and 1670 (C=O) cm^{-1}. Decarboxylation with copper-bronze in quinoline at 180—190° for 1·5 h gave *5-benzyloxy-3-methylbenzo*[b]*thiophen* (90%), b.p. 174° at 1·2 mmHg, m.p. 35—37° (Found: C, 75·4; H, 5·8; S, 12·4%; *M*, 254. $C_{16}H_{14}OS$ requires C, 75·6; H, 5·5; S, 12·6%; *M*, 254).

5-Hydroxy-3-benzo[b]*thienylacetic Acid.*—Solid sodium carbonate was slowly added to a stirred suspension of 5-nitro-3-benzo[*b*]thienylacetic acid (10 g, 0·042 mol) in water (200 ml) at 60° until a clear solution was obtained. Raney nickel (1 g) was added, followed by 100% hydrazine hydrate (10 ml) in portions. When the initial vigorous reaction had subsided, more catalyst (*ca.* 0·25 g) and hydrazine hydrate (5 ml) were added and the mixture was boiled for 1 h. The catalyst was filtered off, the resulting solution was treated with charcoal, cooled in ice, and made acid to litmus with concentrated sulphuric acid. Concentrated sulphuric acid (30 ml) was then added to the stirred solution at 5°, followed by sodium nitrite (3·45 g, 0·05 mol) in water (10 ml). Excess of nitrous acid was destroyed with sulphamic acid and the diazonium solution was added to boiling water (500 ml). The mixture was boiled for 20 min, cooled, and filtered. The filtrate was then shaken with ether (3 × 100 ml), and acidic material was extracted from the ethereal solution with M-sodium carbonate (3 × 100 ml). Acidification of the alkaline solution with

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concentrated hydrochloric acid and extraction with ether gave the required *acid* (5·3 g, 60%) Crystallisation gave pink needles, m.p. 181—183° (from water) (lit.,[18] 174—177°), $\nu_{max.}$ 1705 (C=O), 2400—3200br (OH), and 3280 (phenolic OH) cm^{-1}; δ 7·69 (d, 7-H), 7·46 (s, 2-H), 7·09 (d, 4-H), 6·89 (dd, 6-H), and 3·74 p.p.m. (s, CH_2); $J_{4,6}$ 2·5, $J_{6,7}$ 8·7 Hz.

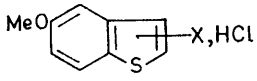
5-Hydroxy-3-benzo[b]*thienylacetamide.*— 5-Hydroxy-3-benzo[*b*]thienylacetic acid (4·2 g, 0·02 mol) was heated under reflux for 8 h with methanol (60 ml) and sulphuric acid (6 ml). The cooled mixture was poured into brine (250 ml) and shaken with benzene (2 × 200 ml). The benzene extract was washed with aqueous sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation gave the *ester* as an oil, which was used without further purification in the next stage (Found: *M*, 222. $C_{11}H_{10}O_3S$ requires *M*, 222), $\nu_{max.}$ 1720 (C=O) and 3410 (phenolic OH) cm^{-1}; δ 7·62 (d, 7-H), 7·31 (s, 2-H), 7·15 (d, 4-H), 6·89 (dd, 6-H), 6·14 (s, OH), 3·76 (s, CH_2), and 3·65 p.p.m. (s, CH_3).

4·9; N, 4·5; S, 10·4%; *M* (free base), 193], $\nu_{max.}$ 2500—3150 (NH_3^+) and 3340 (OH) cm^{-1}; δ 7·73 (d, 7-H), 7·47 (s, 2-H), 7·16 (d, 4-H), 6·94 (dd, 6-H), 6·05 (s, CH·CH), and 3·07 p.p.m. (s, CH_2); $J_{4,6}$ 2·5, $J_{6,7}$ 8·7 Hz.

3-Methyl-7-methylsulphonyloxybenzo[b]*thiophen.*— Methanesulphonyl chloride (7·5 ml) was added dropwise to a stirred solution of 7-hydroxy-3-methylbenzo[*b*]thiophen (1·72 g, 0·01 mol) in dry pyridine at 0°. The mixture was stirred for 1 h and then poured into ice–water. The yellow precipitate (2·4 g, 94%) was collected and crystallised as prisms, m.p. 55° [from acetone–light petroleum (b.p. 40—60°)] (Found: C, 49·4; H, 4·2; S, 26·1. $C_{10}H_{10}O_3S_2$ requires C, 49·6; H, 4·2; S, 26·5%), δ 7·75—7·57 (m, 4-H), 7·5—7·3 (m, 5-H and 6-H), 7·12 (s, 2-H), 3·19 (s, SO_2Me), and 2·42 p.p.m. (s, 3-Me).

3-Bromomethyl-7-methylsulphonyloxybenzo[b]*thiophen.*— *N*-Bromosuccinimide (11·6 g, 0·065 mol) was added to a vigorously stirred solution of 3-methyl-7-methylsulphonyloxybenzo[*b*]thiophen (15·84 g, 0·065 mol) in dry carbon

2- and 3-Substituted-5-methoxybenzo[*b*]thiophen hydrochlorides



			Found (%)				Required (%)		
X	M.p. (°C)	Yield (%)	C	H	N	Formula	C	H	N
2-CH_2·NEt_2	177—178	67	58·8	7·3	4·8	$C_{14}H_{20}ClNOS$	58·8	7·1	4·9
2-CH_2·N[CH_2]$_4$	186—188	90	59·3	6·6	4·9	$C_{14}H_{18}ClNOS$	59·3	6·4	4·9
2-CH_2·NEt·[CH_2]$_2$·OH	112—114	77	55·6	6·8	4·5	$C_{14}H_{20}ClNO_2S$	55·5	6·7	4·6
2-CH_2·NEt·[CH_2]$_2$Cl	156—158	42	52·7	6·3	4·7	$C_{14}H_{19}Cl_2NOS$	52·5	6·0	4·4
2-CH_2·CN *	91—92	53	64·9	4·5	7·1	$C_{11}H_9NOS$	65·0	4·5	6·9
2-[CH_2]$_2$·NH_2	284—285	90	54·3	6·0	5·6	$C_{11}H_{14}ClNOS$	54·2	5·8	5·8
2-[CH_2]$_2$·NH·CO·NH_2 *	168—170	67	57·5	5·7	10·9	$C_{12}H_{11}N_2O_2S$	57·6	5·6	11·2
3-CH_2·NEt·[CH_2]$_2$·OH	124—125	51	55·6	6·6	4·6				
3-CH_2·NEt·[CH_2]$_2$Cl	169—170	56	52·3	5·9	4·1				
3-CH_2·CN *	102—104	68	65·0	4·4	6·7				
3-[CH_2]$_2$·NH_2 †	204—205	92	54·3	5·7	5·8				
3-[CH_2]$_2$·NH·CO·NH_2 *	186—187	73	57·3	5·4	11·1				

* Not hydrochlorides. † δ[$(CD_3)_2SO$] 7·86 (d, 7-H), 7·60 (s, 2-H), 7·52 (d, 4-H), 7·04 (dd, 6-H), 3·87 (s, OMe), and 3·23 p.p.m. (s, CH_2·CH_2); $J_{4,6}$ 2·5, $J_{6,7}$ 8·3 Hz.

The ester was kept overnight with aqueous ammonia (*d*, 0·88; 100 ml) and the resulting *amide* was collected and crystallised as slightly pink needles (3·6 g, 86%), m.p. 180—182° (from propan-2-ol) (Found: C, 58·2; H, 4·6; N, 6·8; S, 15·5%; *M*, 207. $C_{10}H_9NO_2S$ requires C, 58·0; H, 4·4; N, 6·8; S, 15·5%; *M*, 207), $\nu_{max.}$ 1670 (C=O), 3230 and 3350 (NH), and 3400 (OH) cm^{-1}; δ 7·70 (d, 7-H), 7·49br (s, OH), 7·42 (s, 2-H), 7·17 (d, 4-H), 6·95br (s, NH_2), 6·89 (dd, 6-H), and 3·54 p.p.m. (s, CH_2); $J_{4,6}$ 2·5, $J_{6,7}$ 8·3 Hz.

2-(5-Hydroxy-3-benzo[b]*thienyl)ethylammonium Hydrogen Maleate.*—Diborane was prepared by dropwise addition of sodium borohydride (4·5 g) suspended in dry bis-(2-methoxyethyl) ether (50 ml) to the boron trifluoride–ether complex (15·5 g) under dry nitrogen, and was passed into ice-cold tetrahydrofuran (100 ml). 5-Hydroxy-3-benzo[*b*]thienylacetamide (3 g, 0·014 mol) in dry tetrahydrofuran (50 ml) was then added to the stirred solution of diborane and the mixture was boiled for 2 h. A solution of maleic acid (1 g) in dry ethanol (30 ml) was added cautiously to the cooled mixture. The solvent was evaporated and the residue dissolved in dry ethanol (charcoal), and treated with an excess of dry ether. The product (3 g, 67%) was crystallised from dry ethanol–ethyl acetate–ether and gave the *maleate*, m.p. 158—160° (decomp.) [Found: C, 54·5; H, 5·2; N, 4·6; S, 10·2%; *M*, 193. $C_{14}H_{15}NO_5S$ requires C, 54·4; H,

tetrachloride (200 ml) containing a few drops of 60% t-butyl hydroperoxide in dimethyl phthalate. The mixture was irradiated with a 200 W bulb, boiled under reflux for 2 h, cooled, filtered, and concentrated to give the *bromomethyl derivative* (16·8 g, 80%), m.p. 116—118°. It was characterised as its *hexamine salt*, m.p. 148—150° (aqueous acetone) (Found: C, 41·9; H, 4·4; N, 11·9. $C_{16}H_{21}BrN_4O_3S_2$ requires C, 41·65; H, 4·6; N, 12·1%).

3-Cyanomethyl-7-methylsulphonyloxybenzo[b]*thiophen.*— 3-Bromomethyl-7-methylsulphonyloxybenzo[*b*]thiophen (5·62 g, 0·0175 mol) was added to a stirred suspension of potassium cyanide (1·25 g, 0·019 mol) in acetone (25 ml) and water (8 ml). The stirred mixture was boiled under reflux for 22 h, cooled, and poured into ice–water (250 ml) to give a buff solid. The dried material was boiled with carbon tetrachloride (6 × 50 ml) and the combined extracts were concentrated to give the *cyanomethyl compound* (3·3 g, 75%), m.p. 98—99° (from benzene–hexane) (Found: C, 49·4; H, 3·7; N, 5·5. $C_{11}H_9NO_3S_2$ requires C, 49·4; H, 3·4; N, 5·2%), $\nu_{max.}$ 2250 (CN) cm^{-1}.

3-Cyanomethyl-7-hydroxybenzo[b]*thiophen.*— Sodium (0·128 g, 0·056 g atom) was added to a hot solution of 3-cyanomethyl-7-methylsulphonyloxybenzo[*b*]thiophen (7·4 g, 0·028 mol) in dry ethanol (200 ml). The mixture was heated under reflux for 30 min, cooled, and filtered. The

[18] M. Delepine, *Compt. rend.*, 1895, **120**, 501. 1897, **124**, 292.

filtrate was poured into 5% hydrochloric acid (600 ml) and was shaken with ether (3 × 100 ml). Neutral and phenolic fractions were obtained from this ethereal layer in the usual way. 3-*Cyanomethyl-7-hydroxybenzo*[b]*thiophen* (3·57 g, 71%) had m.p. 183—184° (decomp.) (from ethanol–benzene) (Found: C, 63·3; H, 3·8; N, 7·3. $C_{10}H_7NOS$ requires C, 63·5; H, 3·7; N, 7·4%), $\nu_{max.}$ 2260 (CN) and 3325 (OH) cm^{-1}; δ [$(CD_3)_2SO$] 7·66 (s, 2-H), 7·35—7·25 (m, 4-H and 5-H), 6·85 (q, 6-H), and 4·20 p.p.m. (s, CH_2·CN). The neutral component (1·5 g, 26%) was not investigated further although its n.m.r. spectrum appeared to indicate that it was 3-cyanomethyl-7-ethoxybenzo[*b*]thiophen, δ 7·44 (s, 2-H), 7·39—7·20 (m, 4-H and 5-H), 6·85 (d, 6-H), 4·24 (q, CH_2·CH_3), 3·84 (s, CH_2·CN), and 1·49 p.p.m. (t, CH_2·CH_3).

2-(7-*Hydroxy*-3-*benzo*[b]*thienyl*)*ethylamine Hydrochloride*. —A solution of 3-cyanomethyl-7-hydroxybenzo[*b*]thiophen (0·5 g, 0·00265 mol) in dry tetrahydrofuran (30 ml) was added dropwise to a stirred, cooled solution of diborane [prepared by dropwise addition of a fine suspension of sodium borohydride (2·52 g) in dry bis-(2-methoxyethyl) ether (100 ml) to the boron trifluoride–ether complex (3·2 g) in dry ether (20 ml) under dry nitrogen] in dry tetrahydrofuran (150 ml). The mixture was stirred and boiled under nitrogen for 27 h, cooled, and treated cautiously with anhydrous ethanol (3 ml); the *amine hydrochloride* was precipitated by passing dry hydrogen chloride into the clear, yellow solution. The solvents were removed under reduced pressure and crystallisation of the residue gave white needles, m.p. 220—222° (from dry ethanol–ether) [Found: C, 52·75; H, 5·15; Cl, 15·4; N, 6·2%; *M* (free base), 193. $C_{10}H_{12}ClNOS$ requires C, 52·25; H, 5·25; Cl, 15·45; N, 6·1%; *M* (free base), 193], $\nu_{max.}$ 2490—3105 (NH_3^+) and 3240 (OH) cm^{-1}, δ [$(CD_3)_2SO$] 10·40 (s, OH), 9·25br (NH_3^+), 7·53 (s, 2-H), 7·42 (dd, 4-H), 7·26 (t, 5-H), 6·85 (dd, 6-H), and 3·23 p.p.m. (s, CH_2·CH_2); $J_{4.6}$ 1·9, $J_{4.5} = J_{5.6}$ = 8·0 Hz.

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