Novel Tetracycline Analogues. Part 1. Development of a Potential Synthetic Route

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A new type of tetracycline analogue has been designed to incorporate those features of the tetracycline molecule essential for antibacterial activity but with a reduction in structural complexity. These novel analogues are derivatives of 4-dimethylamino-1,4,4a,5,10,10a-hexahydro-3,10a-dihydroxy-1,10-dioxoanthracene-2-carboxamide. An overall synthetic route has been developed involving preparation of 1,2,3,4-tetrahydro-5,8-dimethoxy-4-oxo-2-naphthylacetic acid (3; R^1 = OMe, R^2 = R^3 = R^5 = H, R^4 = Me); variation of the starting material should allow a range of tetracycline analogues to be prepared.

ALTHOUGH semi-synthesis has led to the development of tetracyclines with improved clinical properties,[1] the preparation of totally synthetic analogues has been relatively neglected owing to the complexity of their synthesis, most studies having been directed towards synthesis of the natural antibiotics themselves.[2,3] However, it may be possible to design compounds which are more accessible synthetically yet still incorporate the structural features essential for tetracycline activity. Consideration of the data from semi-synthesis [4] shows that 6-demethyl-6-deoxytetracycline (1) is the simplest tetracycline with antibacterial activity; there are two features essential for this activity. The first is ring A, which must be present intact since deletion of any part of the tricarbonylmethane moiety leads to a total loss of activity and removal of the dimethylamino-group leads to a loss of activity *in vivo* though *in vitro* activity is retained; centres 4a, 5a, and 12a must be in the 'natural' configuration. The second essential feature is the phenol diketone moiety which is involved in chelation with magnesium ions.[5] This chelation is necessary both for uptake of tetracyclines into bacterial cells [6] and for their inhibition of protein synthesis.[7]

Compounds of general structure (2) incorporate both these features and so are potential antibacterial agents of the tetracycline type. Such compounds would be complementary to semi-synthetic tetracyclines, broadening the range of tetracycline analogues. In the development of synthetic routes to this type of compound, elaboration of ring A from precursors of general structure (3) and introduction of the hydroxy-group at the AB ring junction are well documented.[2] The primary concern is therefore development of a general route to the precursor (3): the route must permit incorporation of the amino-substituent in ring A and also permit structural variation in the substituents on ring C. As an initial step, a general synthetic route was explored involving preparation of the model intermediate (3; R^1 = OMe, R^2 = R^3 = R^5 = H, R^4 = Me). The key intermediate in the synthesis is 3-(2,5-dimethoxybenzoyl)glutaric acid (4a), which however could not be prepared by direct acylation of an aromatic precursor. Therefore *p*-dimethoxybenzene was acylated with succinic anhydride [8] and the product methylated to yield methyl 3-(2,5-dimethoxybenzoyl)propionate (4b). This acylation was repeated with 1-phthalimidosuccinic anhydride to check the utility of the scheme for introducing a nitrogen substituent; the analogue (4c) was obtained as expected. There is a possibility of obtaining an isomeric compound (4; R^2 = phthalimido, R^1 = R^3 = R^4 = H), though this is unlikely mechanistically, and also in view of the presence of the bulky phthalimido-group. Comparison of the ^{1}H n.m.r. data with those of compound (4b) confirmed the structure as (4c): the CH_2·C:O signal occurred at δ 3.5 [*cf.* 3.4 for (4b)]. Also, whereas (4b) shows a CH_2·CO_2Me signal at δ 2.7, (4c) exhibits a single proton signal at δ 4.9. The phthalimido-group is stable to subsequent reactions in the scheme envisaged, and so would be expected to act as a precursor of the dimethylamino-group in the ultimate products.

Direct alkylation of methyl 3-(2,5-dimethoxybenzoyl)-propionate (4b) by ethyl bromoacetate was not achieved by using potassium t-butoxide or triphenylmethylpotassium as base. With sodium hydride a product was obtained which however retained the four methylene protons of (4b) (δ 3.3—3.4 and 2.7—2.9) and contained an

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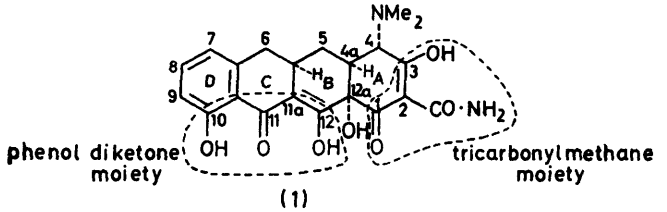
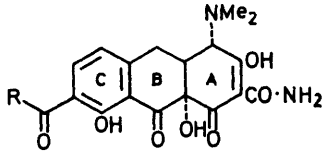
[7] J. P. White and C. R. Cantor, *J. Mol. Biol.*, 1971, **58**, 397.

[8] J. Beraudiat, J. Coillard, and C. Mentzer, *Bull. Soc. chim. France*, 1952, 64.

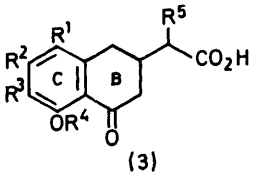
ethyl ester group [δ 4.1—4.3 (2 H, q) and 1.2—1.4 (3 H, t)]; however the n.m.r. spectrum lacked the methyl ester singlet and there was an additional two-proton singlet



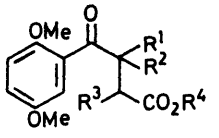
(1)



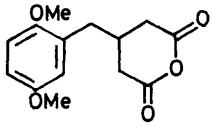
(2)



(3)



(4)a; $R^2 = R^3 = R^4 = H$. $R^1 = CH_2 \cdot CO_2H$
b; $R^1 = R^2 = R^3 = H$, $R^4 = Me$
c; $R^1 = R^2 = R^4 = H$, R^3 = phthalimido
d; $R^1 = R^2 = R^3 = H$, $R^4 = CH_2 \cdot CO_2Et$
e; $R^1 = R^2 = R^3 = H$. $R^4 = Bu^t$
f; $R^1 = CO_2H$. $R^2 = R^3 = H$. $R^4 = Me$
g; $R^1 = CO_2Me$. $R^2 = CH_2 \cdot CO_2Et$. $R^3 = H$, $R^4 = Me$



(5)

at δ 4.6. These data, particularly the excessive deshielding of the isolated methylene group (δ 4.6), are consistent with ethyl 3-(2,5-dimethoxybenzoyl)propionyloxyacetate (4d). This structure was confirmed by mass spectroscopy: the spectrum showed ions due to *successive* fragmentation of the ester functions, with no loss of OMe or CO_2Me. The t-butyl ester (4e) of the starting acid was then subjected to the alkylation reaction with sodium hydride as base, but no product was obtained. Further activation α to the oxo-group was therefore necessary, and this was accomplished by direct carboxylation of methyl 3-(2,5-dimethoxybenzoyl)propionate (4b) with methylmagnesium carbonate.[9] The product, 1-methyl hydrogen 3-(2,5-dimethoxybenzoyl)succinate (4f) showed three carbonyl peaks in the i.r. spectrum. The ^1H n.m.r. spectrum showed a one-proton triplet at δ 4.7 (CH·C:O); *cf.* the two-proton triplet at δ 3.4 in the spectrum of the starting ester (4b). The product (4f) was methylated with diazomethane and alkylated with ethyl bromoacetate and sodium hydride to yield the triester (4g). The ^1H n.m.r. spectrum now lacked the one proton triplet at δ 4.7 but showed characteristic ethyl ester signals and a four-proton singlet at δ 3.15 (2 $CH_2 \cdot CO_2R$). The triester (4g) was then hydrolysed (with concomitant decarboxylation) to 3-(2,5-dimethoxybenzoyl)glutaric acid (4a). The structure was confirmed by the ^1H n.m.r. spectrum, which showed a one-proton triplet at δ 4.1 (CH·C:O) and signals for two acidic protons at δ 9.0 This oxo-acid was reduced and the 3-(2,5-dimethoxybenzyl)-glutaric anhydride (5) prepared. The reduction was monitored (i) by following the disappearance of the u.v. peak at 340 nm and the appearance of a peak at 290 nm, (ii) by the disappearance of the ketone carbonyl band at 1 740 cm^{-1} in the i.r. spectrum, and (iii) by the appearance of a two-proton signal at δ 2.6 in the ^1H n.m.r. spectrum and by the upfield shift of the signal due to the single proton β to the aromatic ring from δ 4.1 to 2.6. Formation of the anhydride (5) was confirmed by the ^1H n.m.r. spectrum, which showed loss of the two exchangeable acidic protons, and by the i.r. spectrum, which showed loss of the OH peak at 3 100—2 500 cm^{-1} and shift of the carbonyl peak from 1 710 cm^{-1} (carboxylic acid) to 1 820 and 1 790 cm^{-1} (typical of anhydrides). Intramolecular acylation of the anhydride (5) then gave the model compound (3; R^1 = OMe, $R^2 = R^3 = R^5$ = H, R^4 = Me). The reaction was monitored by observing the reduction in u.v. absorbance at 290 nm and the appearance of a peak at 340 nm. The ^1H n.m.r. spectrum showed signals for a single acidic proton at δ 8.7 and two aromatic protons at δ 6.8 showing simple *ortho*-coupling.

Further reactions to develop ring A and convert the model precursor into tetracycline analogues of structure (2) are analogous to reactions carried out by Shemyakin's group [2] for the synthesis of anhydrotetracycline from compound (3; R^1 = Me, $R^2 = R^3$ = Ph, R^4 = H, R^5 = phthalimido) and to reactions utilised in the Pfizer–Woodward synthesis of 6-demethyl-6-deoxytetracycline.[10] A relatively direct potential route to tetracycline analogues of structure (2) has therefore been developed; the use of suitable aromatic precursors should lead to a range of compounds suitable for testing for antibacterial activity. Further work in this area is in progress.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^1H N.m.r. spectra were recorded for solutions in $CDCl_3$, unless otherwise stated, with a Perkin-Elmer R12 (60 MHz) or Varian HA 100 (100 MHz) spectrometer (tetramethylsilane as internal standard).

Methyl 3-(2,5-Dimethoxybenzoyl)propionate [8] (4b).—1,4-Dimethoxybenzene (138 g) dissolved in dry dichloromethane

[9] M. Stiles, *J. Amer. Chem. Soc.*, 1959, **81**, 2598.
[10] J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1968, **90**, 439.

(1 300 ml) was cooled to 5 °C and a mixture of anhydrous aluminium chloride (300 g) and succinic anhydride (130 g) was added without allowing the temperature to exceed 10 °C. After 3 days at room temperature the complex was decomposed with ice (1 l) and conc. hydrochloric acid (200 ml), the aqueous layer was extracted exhaustively with ether, and the combined extracts and organic layer from the reaction were extracted with sodium hydroxide solution (2%). The basic extracts were acidified and extracted with ether, and the latter extracts were evaporated *in vacuo* to give an oil which crystallised from water (yield 150 g, 67%); m.p. 102 °C (lit.,[8] 101—102 °C), $\nu_{max.}$ 1780 (C=O), 1 715 (C=O), and 1 610 cm^{-1} (aromatic), δ 10.3 (1 H, s, exchangeable with D_2O), 7.3—6.95 (3 H, m, aromatic), 3.85 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.4 (2 H, t, CH_2·CO), and 2.7 (2 H, t, CH_2·CO_2).

The methyl ester was prepared in 72% yield with diazomethane; m.p. 55 °C, $\nu_{max.}$ 1 730 and 1 660 (C=O), and 1 610 cm^{-1} (aromatic), δ 7.3—6.9 (3 H, m, aromatic), 3.8 (3 H, s, OMe), 3.7 (3 H, s, OMe), 3.6 (3 H, s, CO_2Me), 3.4 (3 H, s, CH_2·CO), and 2.7 (2 H, t, CH_2·CO_2).

3-(2,5-*Dimethoxybenzoyl*)-2-*phthalimidopropionic Acid* (4c).—L-*N*-Phthaloylaspartic anhydride, prepared as reported [11] (yield 74%), had m.p. 219 °C (lit., 219—221 °C). *p*-Dimethoxybenzene (4.8 g) was dissolved in dry dichloromethane (50 ml) and a mixture of anhydrous aluminium chloride (10 g) and L-phthaloylaspartic anhydride (10 g) was added slowly over ½ h, with the temperature kept below 10 °C. The mixture was left at 5 °C for 1 week and then poured onto ice. The lower, organic layer was extracted with sodium hydroxide solution (2%), and the basic extracts were acidified and exhaustively extracted with chloroform; evaporation of the organic extracts *in vacuo* gave the *phthalimido-derivative* as a white solid (3.99 g, 30%), m.p. 149—151 °C, $\nu_{max.}$ 1 740, 1 710, and 1 660 cm^{-1} (C=O), δ[$(CD_3)_2SO$] 8.5 (1 H, s, exchangeable with D_2O), 7.1—7.5 (7 H, m, aromatic), 4.9 (1 H, t, CH), 3.9 (3 H, s, OMe), 3.8 (3 H, s, OMe), and 3.5 (2 H, d, CH_2) (Found: C, 62.9; H, 4.8; N, 3.4%; M^+, 383.0999. $C_{20}H_{17}NO_7$ requires C, 62.6; H, 4.5; N, 3.7%; *M*, 383.1005).

Ethyl [3-(2,5-*Dimethoxybenzoyl*)*propionyloxy*]*acetate* (4d).—Methyl 3-(2,5-dimethoxybenzoyl)propionate (2 g) was dissolved in freshly distilled 1,2-dimethoxyethane (20 ml). A 50% dispersion of sodium hydride in oil (0.33 g) was added, followed over 30 min by a solution of ethyl bromoacetate (1.3 g) in 1,2-dimethoxyethane (10 ml), with the temperature of the mixture maintained between 50 and 60 °C. The mixture was maintained at this temperature with stirring for a further 1 h, then poured into water and extracted with ether. The extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was washed with hexane and the product analysed by g.l.c. [2 m column of 2½% SE 30 on AWDMCS Chromosorb (80—100 mesh) at 225 °C; 27 ml min^{-1} nitrogen carrier gas], which showed a small peak at t_R 6 min (starting material) and a large peak at t_R 22 min. The second component was isolated in a pure state (g.l.c.) by chromatography on silica gel with ether–light petroleum (b.p. 40—60 °C) as eluant. ^1H N.m.r. analysis of the purified product showed an ethyl ester group [δ 4.1—4.3 (2 H, q) and 1.2—1.4 (3 H, t)] but the methylene signals of the starting material were still present [δ 3.3—3.4 (2 H, t) and 2.7—2.9 (2 H, t)]. Additional peaks were at δ 6.9—7.3 (3 H, m, aromatic), 4.6 (2 H, s, CH_2), and 3.75—3.85 (2 × 3 H, s, 2 × OMe). The singlet methylene group at δ 4.6 confirmed the structure (4d). The product showed *m/e* 324 (M^+), 279 ($M - OCH_2CH_3$), 251 ($M - CO_2CH_2CH_3$), 221 ($M - OCH_2CO_2CH_2CH_3$), and 165 ($M - CH_2CH_2CO_2CH_2CO_2CH_2CH_3$), $\nu_{max.}$ 1 670, 1 740, and 1 760 cm^{-1} (C=O) (Found: C, 58.7; H, 6.2. Calc. for $C_{16}H_{20}O_7$: C, 59.2; H, 6.2%).

t-Butyl 3-(2,5-*Dimethoxybenzoyl*)*propionate* (4e).—3-(2,5-Dimethoxybenzoyl)propionic acid (5 g) was suspended in dichloromethane (20 ml) and liquid isobutene (10 g) was added. Concentrated sulphuric acid (1 ml) was then added and the mixture shaken at room temperature in a pressure flask until a clear solution had been formed. The organic solution was washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was recrystallised from light petroleum (b.p. 60—80 °C), yielding cream-coloured *crystals* (δ 3.8 g, 62%), m.p. 70—72 °C, $\nu_{max.}$ 1 720 and 1 660 cm^{-1} (C=O), δ 6.9—7.2 (3 H, m, aromatic), 3.8—3.9 (2 × 3, s, 2 × OMe), 3.2—3.4 (2 H, t, CH_2), 2.5—2.7 (2 H, t, CH_2), and 1.4 (9 H, s, Bu^t) (Found: C, 64.9; H, 7.6%; M^+, 294.1464. $C_{16}H_{22}O_5$ requires C, 65.3; H, 7.5%; *M*, 294.1467).

1-*Methyl Hydrogen* 3-(2,5-*Dimethoxybenzoyl*)*succinate* (4f).—Methyl 3-(2,5-dimethoxybenzoyl)propionate (10 g) was added to a solution of methylmagnesium carbonate [10] in dimethylformamide (100 ml). The mixture was stirred under nitrogen, heated to 110—120 °C, and kept at this temperature for 6 h, with addition of dimethylformamide to maintain constant volume. The viscous mixture was cooled and poured with vigorous stirring into a mixture of ice (200 g) and concentrated hydrochloric acid (20 ml). The mixture was extracted with ether and the extracts then extracted with sodium hydroxide solution (2%). The basic extracts were acidified and extracted with ether, and the bulked ethereal extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The product was crystallised from ether–light petroleum (b.p. 60—80 °C) to give the half-ester (4f) (7.3 g, 60%), $\nu_{max.}$ 1 740, 1 780, and 1 790 (C=O) and 3 100—2 500 cm^{-1} (OH), m.p. 114—116 °C, δ 9.8br (1 H, s, CO_2H), 6.8—7.5 (3 H, m, aromatic), 4.6—4.9 (1 H, t, methine), 3.9 (3 H, s, OMe), 3.8 (3 H, s, OMe), 3.7 (3 H, s, CO_2Me), and 2.9—3.1 (2 H, d, CH_2). The half-ester (4f) was immediately methylated with diazomethane to give the *dimethyl ester* (5.2 g, overall yield 42%), m.p. 74—76 °C, δ 6.8—7.5 (3 H, m, aromatic), 4.6—4.9 (1 H, t, methine), 3.9 (3 H, s, OMe), 3.8 (3 H, s, OMe), 3.7 (2 × 3 H, s, 2 × CO_2Me), and 2.9—3.1 (2 H, d, CH_2) (Found: C, 57.8; H, 5.7%; M^+, 310.1005. $C_{15}H_{18}O_7$ requires C, 58.1; H, 5.8%; *M*, 310.1052).

Ethyl Methyl 3-(2,5-*Dimethoxybenzoyl*)-3-*methoxycarbonylglutarate* (4g).—A 53% dispersion of sodium hydride in oil (2.1 g) was added dropwise to a stirred solution of the foregoing dimethyl ester (6.0 g) in dimethylformamide (50 ml) under nitrogen. A solution of ethylbromoacetate (8.8 g) in dimethylformamide (50 ml) was added over ½ h, and the mixture stirred overnight at room temperature, acidified, poured into water, and extracted with chloroform. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The *product* was washed with hexane and purified by chromatography on silica gel [elution with ether–light petroleum (b.p. 40—60 °C)] (yield 5.2 g, 67%), $\nu_{max.}$ 1 740, 1 760, and 1 790 cm^{-1} (C=O), δ 6.8—7.0 (3 H, m, aromatic), 3.7—4.1 (2 H, q, $MeCH_2$), 3.55 (3 H, s, OMe), 3.6 (3 H, s, OMe), 3.5 (3 H, s, Me), 3.15 (4 H, s, 2 × CH_2), and 0.95—1.22 (3 H, t, CH_3·CH_2) (Found: C, 57.9; H, 6.0%; M^+, 396.1415. $C_{19}H_{24}O_9$ requires C, 57.6; H, 6.0%; *M*, 396.1420).

[11] G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. chim.*, 1960, **79**, 688.

3-(2,5-*Dimethoxybenzoyl*)*glutaric Acid* (4a).—A mixture of the triester (4g) (5 g) in acetic acid (6 ml), conc. sulphuric acid (2 ml), and water (2 ml) was refluxed for 24 h, then poured into water (50 ml) and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*; trituration with ether gave a cream solid which was recrystallised from ether; yield 3 g (80%), m.p. 141—143 °C, $\nu_{max.}$ 1 670, 1 710, and 1 740 (C=O) and 3 100—2 500 cm^{-1} (OH), δ 8.9—9.2 (2 H, s, exchangeable with D_2O), 6.9—7.15 (3 H, m, aromatic), 4.0—4.2 (1 H, t, methine), 3.65 (3 H, s, OMe), 3.75 (3 H, s, OMe), and 2.5—2.8 (4 H, 2 × d, CH_2), M^+ 278.0796 [$C_{14}H_{14}O_6$, corresponding to the anhydride (*M* 278.0790)], *m/e* 278 (*M* − H_2O), 218 (*M* − H_2O − $[CO]_2O$), 204 (*M* − H_2O − $[CO]_2O$ − CH_2), and 165 (*M* − H_2O − $CH[CH_2CO]_2O$).

3-(2,5-*Dimethoxybenzyl*)*glutaric Anhydride* (5).—3-(2,5-Dimethoxybenzoyl)glutaric acid (3 g) was added to zinc amalgam (10 g) and conc. hydrochloric acid (10 ml); the mixture was heated under reflux for 16 h, allowed to cool, and extracted with ethyl acetate. The bulked extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield 3-(2,5-*dimethoxybenzyl*)*glutaric acid* (2.8 g, 94%), $\nu_{max.}$ 1 710 (C=O) and 3100—2500 cm^{-1} (OH), δ $[(CD_3)_2CO]$ 9.3—9.5 (2 H, s, exchangeable with D_2O), 6.6—6.8 (3 H, m, aromatic), 3.65 (3 H, s, OMe), 3.6 (3 H, s, OMe), 2.5—2.7 (3 H, m, CH_2 + CH), and 2.2—2.4 (4 H, m, 2 × CH_2). The acid was heated under reflux with acetic anhydride (35 ml) for 1 h. The excess of acetic anhydride was evaporated off under reduced pressure to yield the *anhydride* (5), $\nu_{max.}$ 1820 and 1 790 cm^{-1} (anhydride C=O) (Found: C, 63.3; H, 6.0%; M^+, 264.1003. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%; *M*, 264.0998).

1,2,3,4-*Tetrahydro*-5,8-*dimethoxy*-4-*oxo*-2-*naphthylacetic Acid* (3; R^1 = OMe, R^2 = R^3 = R^5 = H, R^4 = Me).—The anhydride (5) (2.5 g) was dissolved in dichloromethane (20 ml). Nitrobenzene (10 ml) and anhydrous aluminium chloride (4 g) were added slowly over ½ h, with the temperature maintained below 10 °C. The mixture was kept at room temperature for 48 h and poured onto ice (40 g). The aqueous layer was extracted with ethyl acetate and the bulked extracts and the organic layer from the original mixture were extracted with sodium hydroxide solution (2%). The combined basic extracts were acidified and extracted with ethyl acetate; the latter extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield the required acid, $\nu_{max.}$ 1 710 and 1 730 cm^{-1} (CO), δ 8.6—8.7 (1 H, s, exchangeable with D_2O), 6.8—6.9 (2 H, d, aromatic), 3.7 (3 H, s, OMe), 3.6 (3 H, s, OMe), 2.3—2.8 (3 H, m, CH_2 + CH), and 2.1—2.3 (4 H, m, 2 × CH_2). The acid forms a resin in air; it was characterised as its *methyl ester* (prepared with diazomethane) [1.1 g, overall yield 34% from (5)], m.p. 105 °C, $\nu_{max.}$ 1 710 and 1 730 cm^{-1} (C=O), δ 6.8—6.9 (2 H, d, aromatic), 3.7 (3 H, s, OMe), 3.6 (3 H, s, OMe), 3.5 (3 H, s, CO_2Me), 2.3—2.8 (3 H, m, CH_2 + CH), 2.1—2.3 (4 H, m, 2 × CH_2) (Found: C, 64.4; H, 6.2%; M^+, 278.1143. $C_{15}H_{18}O_5$ requires C, 64.8; H, 6.0%; *M*, 278.1154).

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