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Influence of the vinyl group on the calcium antagonistic activity of analogues of Fostedil

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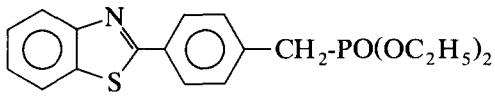
Abstract

Four aryl vinyl diethyl benzylphosphonates related to Fostedil were synthesized and evalued for their in vitro calcium-inhibitory activity. None of these compounds exhibited any calcium antagonistic profile. Unlike a series of diethyl-styryl benzylphosphonates, previously described, the presence of two aromatic rings linked by a vinyl group did not improve the calcium antagonistic activity.

Key words: Calcium antagonist; Diethyl benzylphosphonate; Vinyl group

1. Introduction

Fostedil: 4-(2-benzothiazolyl) diethyl benzylphosphonate, was described as a new calcium antagonist (Morita et al., 1982; Kanebo Ltd Patent, 1983).



Fostedil

It has been shown that substitution of the benzothiazole ring with various substituents did not enhance the coronary vasodilatory activity of Fostedil in the isolated guinea pig heart (Yoshino et al., 1986). But, in the same work, the authors showed that the diethyl phosphonate moiety played an important role in the activity. This fact was also established in our laboratory (Mouysset et al., 1990).

In a previous study (Mouysset et al., 1987), we fixed directly the diethyl methyl phosphonate group onto oxygenated heterocyclic compounds known for their cardiovascular tropism; but none of them exhibited any activity on the inhibition of the contraction of rabbit aortal strips test. Nevertheless, the insertion of a phenyl group between the diethyl methyl phosphonate and the heterocyclic moieties, so as to come nearer to the Fostedil structure, recently led us to compounds which were as potent as Fostedil. For instance, 4-(2-benzofuryl) diethyl benzylphosphonate exhibited a slightly stronger calcium antagonistic activity than Fostedil (Baziard-Mouysset et al., 1993).

These results suggested that the presence of two aromatic systems also seemed required for activity. This finding was verified in another recent study (Tchani et al., 1992): among various substituted diethyl benzylphosphonates, the styryl-substituted compound was the strongest. We have hence constated the benefit of the vinyl junction between the two aromatic parts.

In an attempt to confirm or invalidate this assumption, we have incorporated the vinyl group between various bicyclic systems and the diethyl benzylphosphonate moiety (Fig. 1). It should be noted that in the case of benzofurane and benzothiazole (Fostedil) bicyclic

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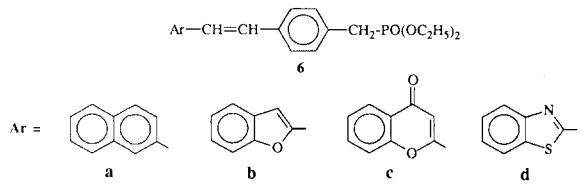


Fig. 1.

systems, the corresponding products without vinyl junction already exhibited a good calcium antagonistic profile.

2. Chemistry

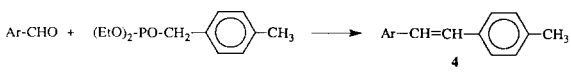
The 2-(4-methyl styryl) derivatives **4** which are used as intermediates are synthesized either by using a specific method (**4b**, **4c**, **4d**) or via the Wittig–Horner reaction (Horner et al., 1959) by action of the corresponding aldehyde with 4-methyl benzyl diethyl phosphonate, as shown in Scheme 1.

This method was used to prepare the derivative **4a** and as an alternative for the **4b** one. In fact, the 2-(4-methyl styryl) benzofurane **4b** can also be obtained via an intramolecular Wittig reaction (Hercouet and Le Corre, 1979) by condensing 4-methyl cinnamoyl chloride **1** with ortho hydroxybenzyl triphenyl phosphonium bromide. This latter compound can be obtained by reaction of triphenyl phosphine hydrobromide with saligenol.

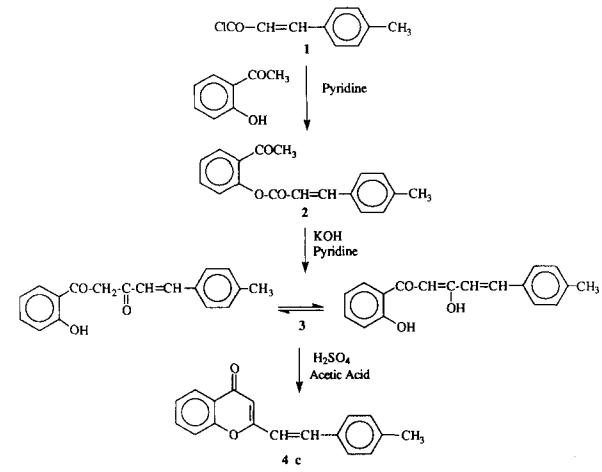
2-(Methyl styryl) chromone **4c** was prepared by the route shown in Scheme 2. Orthohydroxy acetophenone was first esterified with 4-methyl cinnamoyl chloride **1** in pyridine. The resulting ester **2** gave rise by Baker–Venkataraman transposition (Baker, 1933) to ω-paramethyl cinnamoyl 2-hydroxy acetophenone **3**. The cyclized form **4c** was then yielded by heating **3** in the presence of sulfuric acid.

Condensation under reflux of 4-methyl cinnamoyl chloride **1** with 2-amino thiophenol in dimethylformamide (DMF) gave 2-(4-methyl styryl) benzothiazole **4d** (Rastogi and Sharma, 1982).

Phosphonate synthesis was conducted as shown in Scheme 3: the bromomethyl derivatives **5** were obtained by free radical bromination (Jarvis and Saukaitis, 1973) of the methyl compounds **4** with N-bromosuccinimide (NBS). The diethyl phosphonates **6** were prepared via the Michaelis–Arbuzov reaction (Arbuzov, 1964) by heating the halogen derivatives **5** with triethyl phosphite (TEP).

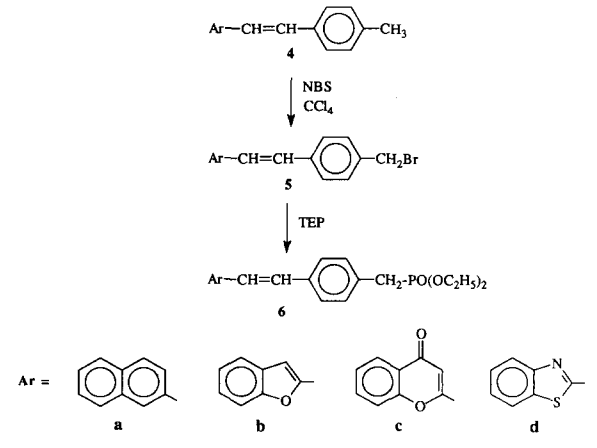


Scheme 1.



Scheme 2.

In the case of compounds **4b**, **4c**, **5b**, **5c**, **6b** and **6c**, analysis of proton NMR spectra showed that ethylene proton signals can exist either as a single or a double doublet — one of them may sometimes be blurred with the aromatic protons — with a coupling constant of about 16 Hz. This indicated that these compounds exhibited an E configuration. In the case of compounds **4a**, **4d**, **5a**, **5d**, **6a** and **6d**, either the magnetic equivalence of ethylene protons or else the complexity of the spectrum did not permit identification of their configuration. Nevertheless, a careful examination of the 200-MHz proton NMR spectrum of **6a**, showed at δ 7.11, a false singlet which was in fact a degenerate doublet with a coupling constant of about 16.5 Hz. On the



Scheme 3.

other hand, **4d** and **4c** synthesis was performed from E paramethylcinnamic acid; one can reasonably assign the E configuration to all of our ethylenic compounds.

3. Pharmacology

The calcium antagonistic activity of compounds **6** was assayed in vitro by examining the reduction in contraction of rabbit aortic fragments in the presence of calcium chloride. All the compounds were tested on three aortic fragments at a concentration of 0.50 μg/ml. The mean values of the results were expressed as the percentage of relaxation.

The experimental protocol was identical to that already described (Mouysset et al., 1987) and based on that of Polster (Polster and De Claviere, 1981).

4. Results and discussion

The pharmacological properties of vinyl compounds **6** are shown in Table 1. Activity of non-vinylic analogues (Z = Ø) previously studied (Tchani et al., 1992; Baziard-Mouysset et al., 1993) is also reported for comparison.

Introduction of the vinyl group between the phenyl and the diethyl benzylphosphonate moieties was shown to enhance about two-fold the calcium antagonistic activity of the basic diphenyl compound (−12 vs −29). This observation gave rise to our motivation (Tchani et al., 1992). But insertion of the vinyl group between the diethyl benzylphosphonate moiety and bicyclic or heterocyclic systems to give compound **6** did not lead to increased activity. On the contrary, in the case of the benzofuran and benzothiazole (Fostedil) derivatives, which exhibited excellent calcium antagonism (−62 and −57 respectively), the introduction of the vinyl group to give **6b** and **6d** led to a loss of activity. This fact could be explained by the requirement of an optimal distance between the phenyl included in the heterocycle and the diethyl benzylphosphonate moiety. Introduction of the vinyl fragment would lead to a too large distance and accordingly to a loss of activity. Effectively, introduction of a second vinyl group between the two phenyl groups (Z = $(CH{=}CH)_2$) was shown to result in a loss of activity.

Moreover, one can consider styryl benzylphosphonate previously described (Tchani et al., 1992) as an analogue of Fostedil, while vinyl derivatives **6** could be assimilated to analogues of the inactive diene compound.

Table 1
In vitro calcium antagonistic activity of compounds **6** and of their non-vinyl analogues: reduction of the contraction of rabbit aortal strips at 0.5 μg/ml in the presence of calcium chloride

Ar	Z = Ø	Z = CH=CH		Z = $(CH{=}CH)_2$
Phenyl	−12 [a]	−29 [a]		+1 [a]
2-Naphtyl	–	−2	**6a**	–
2-Benzofuranyl	−62 [b]	−6	**6b**	–
2-Benzogammapyronyl	0 [b]	−2	**6c**	–
2-Benzothiazolyl	−57 [c]	−7	**6d**	–

[a] Tchani et al. (1992); [b] Baziard-Mouysset et al. (1993); [c] Fostedil: type sample.

5. Experimental procedures

Purity of compounds was systematically checked by TLC on Merck 60 F 254 silica gel.

Melting points were taken on a Kofler hot stage apparatus. Infrared spectra were recorded on a Perking-Elmer 983G spectrometer, samples were included in solid KBr pellets. ^{1}H NMR spectra were recorded either at 60 MHz with a Varian T60 apparatus or at 200 MHz with a Bruker 200 spectrometer. Chemical shifts are in δ, parts per million (ppm) with regard to Tetramethylsilane (TMS) used as internal standard. Elemental analysis were within ±0.4% and are not published.

4-Methyl cinnamoyl chloride ***1***

To a solution of E 4-methyl cinnamic acid (16.2 g, 0.1 mole) in cyclohexane (200 ml), was added thionyl chloride (15 g, 0.13 mole). The reaction mixture was refluxed for 3 h, then cooled and evaporated under reduced pressure, to give white needles (19 g).

$C_{10}H_9ClO$, mw: 180.5, mp: 70–72°C,

quantitative yield

IR (KBr) (cm^{-1}):

3125, 3057, 3024, 2921, 2852 (CH_3, CH);

1738, 1713 (C=O); 1629, 1617, 1564 (C=C).

^{1}H NMR ($CDCl_3$) (δ ppm): 2.47 (s, 3H, CH_3);

6.17 (d, 1H, CH–Ar; J = 16 Hz);

7.13–7.60 (m, 4H, arom);

7.90 (d, 1H, CH–CO; J = 16 Hz).

2-(4-Methyl cinnamoyloxy)acetophenone ***2***

A solution of chloride **1** (20 g, 0.11 mole) and 2-hydroxyacetophenone (13.6 g, 0.1 mole) in pyridine

(200 ml) was stirred at room temperature for 45 min. The reaction mixture was then poured into 500 ml of 5% hydrochloride acid. After stirring for 10 min, the resulting white precipitate was filtered and washed, first with a small amount of methanol, then with water (25 ml). The pale beige compound collected was recrystallized from about 200 ml of methanol.

$C_{18}H_{16}O_3$, mw: 280, yield: 97%, mp: 98°C

IR (KBr) (cm^{-1}): 3074, 3023, 3003,
2922 (CH_3, CH); 1721 (COO); 1679 ($COCH_3$);
1601, 1569, 1509, 1480, 1450 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 2.43 (s, 3H, CH_3);
2.56 (s, 3H, $COCH_3$);
6.56 (d, 1H, CH–Ar; J = 16 Hz);
7.31–8.00 (m, 8H, arom);
7.93 (d, 1H, CO–CH; J = 16 Hz).

ω-Para methyl cinnamoyl 2-hydroxyacetophenone 3

A solution of 2-(4-methyl cinnamoyloxy) acetophenone **2** (14 g, 0.05 mole) in pyridine (100 ml) was heated in an oil bath at 70°C. Finely ground KOH (20 g, 0.36 mole) was then added and the mixture stirred for 15 min. After cooling, the resulting solution was acidified with an excess of 10% acetic acid (about 200 ml). The yellow precipitate which formed was filtered, washed with water and recrystallized from methanol (200 ml).

$C_{18}H_{16}O_3$, mw: 280, yield: 75%, mp: 115°C

IR (KBr) (cm^{-1}):
3431 (OH); 3041, 2887 (CH_3, CH);
1714, 1624 (CO); 1569, 1555, 1485 (C=C).

^1H NMR ($CDCl_3$) (δ ppm):
2.40 (s, 3H, CH_3); 6.32 (s, 1H, CH–CO);
6.51 (d, 1H, CH–Ar; J = 16 Hz);
6.81–7.83 (m, 9H, CH and arom);
12.2 (s, 1H, OH, phenol); 14.73 (s, 1H, OH, enol).

(It should be noted that this spectrum squares with the enol form.)

*Synthesis of compounds **4a** and **4b** via the Wittig–Horner reaction*

2-Naphtaldehyde is commercially available and benzofurane-2-carboxaldehyde was synthesized according to a method previously described (Payard and Couquelet, 1979).

Aldehyde (0.4 mole) was added dropwise to a solution of 50% sodium hydride (0.05 mole) in mineral oil, previously washed with cyclohexane and paramethyl diethyl benzylphosphonate (9.68 g, 0.04 mole) in distilled and dry dimethoxyethane (DME) (200 ml). The mixture was stirred at room temperature for 10 h. Methanol (10 ml) was added to destroy the excess of sodium hydride and the mixture poured onto water (500 ml). After filtration and drying, the crude product was recrystallized from ethanol.

*2-(4-Methyl styryl) naphtalene **4a***

$C_{19}H_{16}$, mw: 244, yield: 75%, mp: 210°C

IR (KBr) (cm^{-1}): 3089, 3081, 3050, 3017, 2977, 2964,
2912 (CH_3, CH); 1603, 1589, 1568, 1508 (C=C).

^1H NMR (DMSO-d_6) (δ ppm): 2.49 (s, 3H, CH_3);
6.96–7.99 (m, 13H, CH=CH and arom).

*2-(4-Methyl styryl) benzofurane **4b***

$C_{17}H_{14}O$, mw: 234, yield: 75%, mp: 145°C

IR (KBr) (cm^{-1}): 3024, 2955, 2915, 2893
(CH_3, CH); 1602, 1511 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 2.45 (s, 3H, CH_3);
6.53 (s, 1H, H_3); 6.91 (d, 1H; J = 16 Hz, CH–Ph);
7.15–7.50 (m, 9H, CH–Ar, arom).

*2-(4-Methyl styryl) benzofurane **4b** (second method)*

A solution of ortho hydroxybenzyl triphenyl phosphonium (22.45 g, 0.05 mole), 4-methyl cinnamoyl chloride **1** (13.53 g, 0.075 mole) and pyridine (7.90 g, 0.10 mole) in chloroform (50 ml) was heated under reflux (Burali et al., 1987). After adding 300 ml of toluene, 150 ml of solvent was evaporated so as to eliminate the greater part of chloroform. Triethylamine (15.15 g, 0.15 mole) was then added and the reaction mixture heated under reflux for 2 h. After filtration of triethylamine hydrobromide, toluene was evaporated under reduced pressure. The yellow crude product was recrystallized from ethanol and dried to give 16 g of **4b**.

Yield = 69%;

Chemical and physical properties: see above.

*2-(4-Methyl styryl) chromone **4c***

A solution of ω-aroyl 2-hydroxy acetophenone **3** (8.4 g, 0.03 mole) in acetic acid (80 ml) and sulfuric acid (1.75 ml) was heated at 100°C for 1 h while stirring.

The mixture was then poured onto 250 g of ice under vigorously stirring. The crude product was then washed with water until neutrality of washing water and recrystallized from 150 ml of cyclohexane.

$C_{18}H_{14}O_2$, mw: 262, yield: 80%, mp: 159°C

IR (KBr) (cm^{-1}): 3021, 2971, 2869 (CH_3, CH); 1641 (CO); 1621, 1587, 1558, 1505 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 2.43 (s, 3H, CH_3); 6.33 (s, 1H, H_3); 6.70 (d, 1H, CH–Ph; J = 16 Hz); 7.10–7.87 (m, 8H, CH–Ar, arom); 8.06 (dd, 1H, H_5; J = 8 and 2 Hz).

2-(4-Methyl styryl) benzothiazole ***4d***

A solution of 4-methyl cinnamoyl chloride **1** (12 g, 0.066 mole) and 2-amino thiophenol (8.31 g, 0.066 mole) in distilled and dry DMF (100 ml) was refluxed for 20 h. After cooling, the solution was added to 250 ml of distilled water. The residue was filtered, washed with a solution of $NaHCO_3$ and recrystallized from 250 ml of ethanol, to give 9.75 g of pearly needles.

$C_{16}H_{13}NS$, mw: 251, yield: 68%, mp: 142°C

IR (KBr) (cm^{-1}): 3165, 3133, 3079, 3056, 3033, 2992, 2909 (CH_3, CH); 1640, 1601, 1545, 1512, 1477 (C=N, C=C).

^1H NMR ($CDCl_3$) (δ ppm): 2.36 (s, 3H, CH_3); 6.90–7.99 (m, 10H, CH=CH, arom).

Synthesis of bromomethyl derivatives ***5***

Corresponding methyl derivative **4** (0.05 mole) was dissolved in carbone tetrachloride (150 ml). The solution was heated for 30 min. Then, NBS (9.9 g, 0.056 mole) and a catalytic amount of azo bis isobutyronitrile (AIBN) (1.5 to 2 g) were added. The mixture was refluxed for 6 h. After a weak cooling, the succinimide was filtered. The filtrate was then cooled to obtain the bromomethyl derivative, which crystallized. If necessary, the solvent was evaporated and recrystallization could be performed from ethanol.

2-(4-Bromomethyl styryl) naphtalene ***5a***

$C_{19}H_{15}Br$, mw: 323, yield: 43%, mp: 162°C

IR (KBr) (cm^{-1}): 3054, 3023, 2963 (CH_2, CH); 1624, 1592, 1567, 1507 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 4.51 (s, 2H, CH_2Br); 7.01–8.13 (m, 13H, CH=CH and arom).

2-(4-Bromomethyl styryl) benzofurane ***5b***

$C_{17}H_{13}BrO$, mw: 313, yield: 53%, mp: 88–90°C

IR (KBr) (cm^{-1}): 3163, 3085, 3057, 2974, 2925, 2895 (CH_2, CH); 1631, 1606, 1572 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 4.50 (s, 2H, CH_2Br); 6.53 (s, 1H, H_3); 6.91 (d, 1H, CH–Ph; J = 16 Hz); 7.15–7.50 (m, 9H, CH–Ar, arom).

2-(4-Bromomethyl styryl) chromone ***5c***

$C_{18}H_{13}BrO_2$, mw: 341, yield: 69%, mp: 140°C

IR (KBr) (cm^{-1}): 3060, 2922 (CH_2, CH); 1644 (CO); 1557, 1511, 1495 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 4.50 (s, 2H, CH_2Br); 6.33 (s, 1H, H_3); 6.73 (d, 1H, CH–Ph; J = 16 Hz); 7.17–7.83 (m, 8H, CH and arom); 8.17 (dd, 1H, H_5; J = 8 and 2 Hz).

2-(4-Bromomethyl styryl) benzothiazole ***5d***

$C_{16}H_{12}BrNS$, mw: 330, yield: 63%, mp: 157°C

IR (KBr) (cm^{-1}): 3142, 3029, 2995 (CH_3, CH_2, CH); 1627, 1554, 1511, 1479 (C=C).

^1H NMR ($CDCl_3$) (δ ppm): 4.43 (s, 2H, CH_2Br); 7.10–8.02 (m, 10H, CH=CH and arom).

Diethyl phosphonates ***6***

A solution of corresponding bromomethyl derivative **5** (0.02 mole) in TEP (4.15 g, 0.025 mole) was heated under reflux at 140°C for 6 h. The excess of TEP was removed under reduced pressure. The resulting viscous oil was chromatographed on silicagel column, using at first 1,2-dichloroethane (DCE), then ethyl acetate as eluents. Compounds **6** were recrystallized from ethyl acetate.

4-[2-(2-Naphtyl) vinyl] diethyl benzylphosphonate ***6a*** *(Eiichi et al., 1976)*

$C_{23}H_{25}O_3P$, mw: 380, yield: 78%, mp: 95°C

IR (KBr) (cm^{-1}): 3092, 3083, 3063, 3053, 3027, 3015, 2979 (CH_3, CH_2, CH); 1602, 1594, 1556, 1509 (C=C); 1245 (P=O).

^{1}H NMR ($CDCl_3$) (δ ppm):

1.23 (t, 6H, CH_3; J = 7 Hz);

3.13 (d, 2H, CH_2–P; J = 22 Hz);

4.06 (m, 4H, CH_2–O; J = 7 Hz);

7.11 (false singlet, degenerate doublet, 2H, CH=CH; J = 16.5 Hz); 7.33–7.95 (m, 11H, arom).

4-[2-(2-Benzofuryl) vinyl] diethyl benzylphosphonate ***6b***

$C_{21}H_{23}O_4P$, mw: 370, yield: 65%, mp: 106°C

IR (KBr) (cm^{-1}): 3125, 3037, 2979, 2952, 2925, 2864 (CH_3, CH_2, CH); 1629, 1602, 1565 (C=C); 1244 (P=O).

^{1}H NMR ($CDCl_3$) (δ ppm):

1.30 (t, 6H, CH_3; J = 7 Hz);

3.20 (d, 2H, CH_2–P; J = 22 Hz);

4.15 (m, 4H, CH_2–O; J = 7 Hz);

6.53 (s, 1H, H_3); 6.91 (d, 1H, CH–Ph: J = 16 Hz);

7.15–7.50 (m, 9H, CH–Ar, arom).

4-[2-(2-Benzogammapyronyl) vinyl] diethyl benzylphosphonate ***6c***

$C_{22}H_{23}O_5P$, mw: 398, yield: 76%, mp: 103°C

IR (KBr) (cm^{-1}): 3073, 2977, 2905 (CH_3, CH_2, CH); 1634 (CO); 1589, 1564, 1510, 1473 (C=C); 1247 (P=O).

^{1}H NMR ($CDCl_3$) (δ ppm):

1.33 (t, 6H, CH_3; J = 7 Hz);

3.23 (d, CH_2–P; J = 21 Hz);

4.17 (m, 4H, CH_2–O; J = 7 Hz);

6.33 (s, 1H, H_3); 6.80 (d, 2H, CH–Ar; J = 16 Hz);

7.20–7.83 (m, 8H, CH–Ar, arom);

8.16 (dd, 1H, H_5; J = 8 and 2 Hz).

4-[2-(2-Benzothiazolyl) vinyl] diethyl benzylphosphonate ***6d***

$C_{20}H_{22}NO_3PS$, mw: 387, yield: 82%, mp: 101°C

IR (KBr) (cm^{-1}): 3190, 3058, 3025, 2982, 2910 (CH_3, CH_2, CH); 1603, 1554, 1512 (C=C); 1240 (P=O).

^{1}H NMR ($CDCl_3$) (δ ppm):

1.33 (t, 6H, CH_3; J = 7 Hz);

3.10 (d, 2H, CH_2–P; J = 22 Hz);

4.05 (m, 4H, CH_2–O; J = 7 Hz);

7.02–8.00 (m, 10H, CH=CH and arom).

References

Arbuzov, B.A. (1964) Michaelis–Arbuzov and Perkov reactions. Pure Appl. Chem. 9, 307–335.

Baker, W. (1933) Molecular rearrangement of some o-acyloxyacetophenones and the mechanism of the production of 3-acylchromones. J. Chem. Soc. 1381–1389.

Baziard-Mouysset, G., Tchani, G.W., Stigliani, J.L., Payard, M., Bonnafous, R. and Tisne-Versailles, J. (1993) Synthesis and calcium antagonistic activity of a series of diethyl benzofuryl, benzothienyl and benzogammapyronyl benzylphosphonates. Eur. J. Med. Chem., 28: 539–546.

Burali, C., Desideri, N., Stein, L., Conti, C. and Orsi, N. (1987) Synthesis and anti-rhinovirus activity of halogen-substituted isoflavenes and isoflavans. Eur. J. Med. Chem. 22, 119–123.

Eiichi, O., Ryuichi, M., Kisuke, O. and Ichoro, O. (1976) Styryltriazole fluorescent whitening agents. Jpn Kokai 75, 126, 743 (Cl. C08KL, C09K, B05D, D01F), 06 Oct. 1975, Appl. 74 28, 133, 13 Mar. 1974; 8 pp. (CA (1976) 84: 32606c).

Hercouet, A. and Le Corre, M. (1979) Une nouvelle voie d'accès aux benzofurannes. Tetrahedron Lett. 23, 2145–2148.

Horner, L., Hoffman, H., Wippel, H.G. and Klahre, G. (1959) Phosphinoxyde als olefinierungsreagenzien. Chem. Ber. 92, 2499–2505.

Jarvis, B. and Saukaitis, J.C. (1973) Nucleophilic Displacements on halogen atoms. II. Kinetic study of the reactions of α-halo sulfones with triphenylphosphine. J. Am. Chem. Soc. 95, 7708–7715.

Kanebo Ltd (1983) (p-2-benzothiazolylbenzyl) phosphonate esters. Jpn Kokai Tokyo Koho JP 57, 150, 698 [82, 150, 698] (Cl. C07F9/65) 17 Sept. 1982 (CA (1983) 98: 72444u).

Morita, T., Yoshino, K., Kanazawa, T., Ito, K. and Nose, T. (1982) Vasodilator action of KB-944, a new calcium antagonist. Arzneim. Forsch./Drug Res. 32, 1037–1088.

Mouysset, G., Bellan, J., Payard, M. and Tisne-Versailles, J. (1987) Recherche d'inhibiteurs calciques en série hétérocyclique oxygénée. Farmaco Ed. Sci. 42, 805–813.

Mouysset, G., de Saqui-Sannes, G., Younes, S., Bellan, J., Payard, M. and Tisne-Versailles, J. (1990) Contribution of the diethyl phosphonate group to a first approach of calcium-inhibiting activity: study of a series of various substituted 2-phenylbenzothiazoles. Farmaco Ed. Sci. 45, 945–952.

Payard, M. and Couquelet, J. (1979) A new and facile synthesis of 2-hydroxymethylchromone and 2-formylchromone. Synthesis 77, 889.

Polster, M. and De Claviere, P. (1981) Calcium-antagonistic effects of L 9394 on vascular and ventricular muscle. Biochem. Pharmacol. 30, 897–901.

Rastogi, R. and Sharma, S. (1982) Synthesis of 2-substituted benzofurans as potential anthelmintics. Indian J. Chem. 21B, 485–487.

Tchani, G., Baziard-Mouysset, G., Younes, S., Bellan, J., Payard, M., Stigliani, J.L., Grassy, G., Bonnafous, R. and Tisne-Versailles, J. (1992) Evaluation de l'activité inhibitrice calcique d'une série de benzylphosphonates de diéthyle. Eur. J. Med. Chem. 27, 845–850.

Yoshino, K., Kohno, T., Uno, T., Morita T. and Tsukamoto, G. (1986) Organic phosphorus compounds. I. 4-(benzothiazol-2-yl) benzylphosphonates as potent calcium antagonistic vasodilator. J. Med. Chem. 29, 820–825.