SYNTHESIS OF [TRIAZOLE-3(5)-^{14}C]-PROPICONAZOLE STEREOISOMERS

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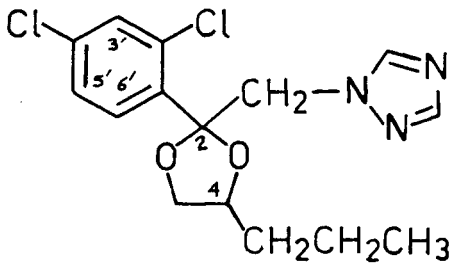
SUMMARY

A preparation of all four stereoisomers of the fungicide and sterol biosynthesis inhibitor propiconazole (1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole), labelled with [^{14}C] in the triazole ring, is described.

Key Words - 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole; propiconazole; [3(5)-^{14}C]-1,2,4-triazole; chiral synthesis.

INTRODUCTION

Propiconazole, (1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole) (**1**), is a fungicide in widespread use in agriculture, primarily to combat diseases of cereals (1). The molecule (**1**) contains two chiral centres and therefore propiconazole exists as four



a	2R, 4R
b	2R, 4S
c	2S, 4R
d	2S, 4S

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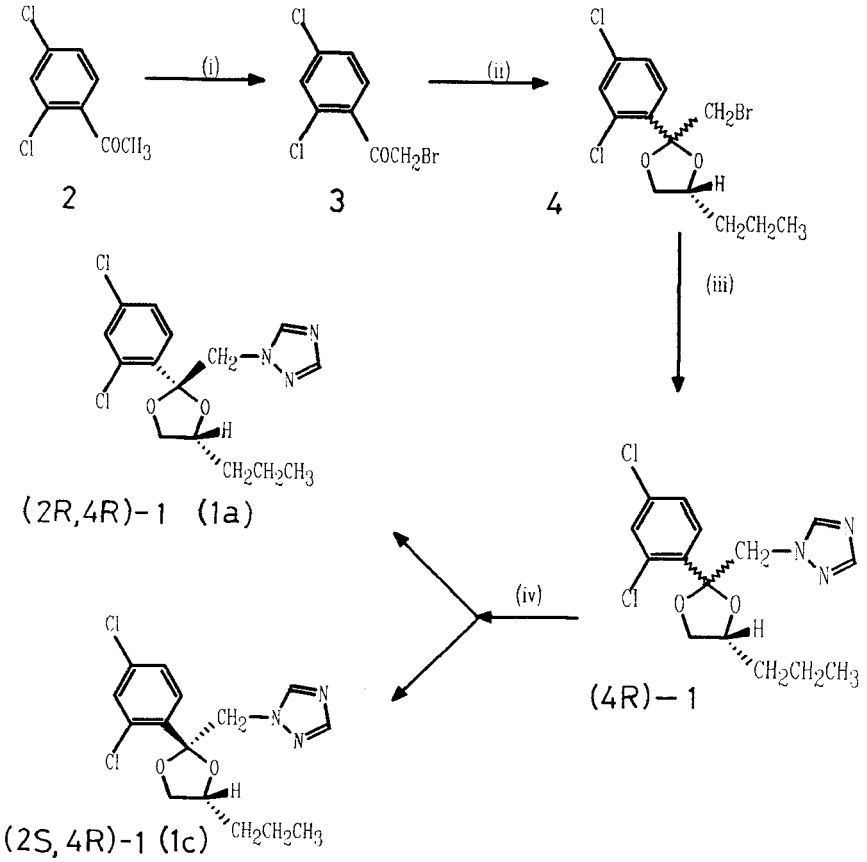
0362–4803/92/070545–07$08.50

Received 24 February, 1992
Revised 29 March, 1992

stereoisomers, comprising two diastereoisomeric pairs of enantiomers (2R,4S and 2S,4R, and 2S,4R, and 2R,4R and 2S,4S, respectively). In connection with studies of the uptake, translocation and metabolism of the separate stereoisomers of propiconazole in plants, we required the four stereoisomers in high purity, labelled with ^{14}C. Published methods for the preparation of propiconazole stereoisomers (2) were not suitable for radiosynthesis, and we devised a convenient synthesis of each of the stereoisomers **1a-1d** labelled with ^{14}C in the triazole ring.

Scheme 1.



Reagents and conditions: (i) Br_2/HOAc; (ii) (R)-pentane-1,2-diol, TosOH, toluene, rfx.; (iii) [3(5)-^{14}C]-triazole, KOH, DMSO, 144°; (iv) flash chromatography. The (2R, 4S) and (2S, 4S) isomers (**1b** and **1d** respectively) were prepared analogously starting from (S)-pentane-1,2-diol.

RESULTS AND DISCUSSION

The route chosen for the synthesis of the four stereoisomers of [triazole-3(5)-^{14}C]-propiconazole is shown in Scheme 1. Chirality at C-4 of the dioxolane ring was fixed from the outset by the choice of the appropriate enantiomerically pure pentane-1,2-diol; the preparation of the (4R) and (4S) compounds was carried out in parallel. The bromoketone (**3**), required as starting material for both series of compounds, was obtained by bromination of 2,4-dichloroacetophenone (**2**). Conventional methods for preparation of bromoacetophenones (3,4) gave products contaminated with substantial amounts of the dibromoketone, which was difficult to remove. Bromination of 2,4-dichloroacetophenone by the standard method (4), but using only half an equivalent of bromine, gave a product which could be purified by distillation under reduced pressure. Formation of the dioxolane ring (Scheme 1, step (ii)) introduces a second chiral centre at C-2, yielding a diastereoisomeric pair of bromomethyl dioxolanes (**4**). We found it most convenient to leave the separation of the diastereoisomeric mixture until after introduction of the triazole, when it proved possible to separate the (2R) and (2S) isomers by preparative TLC. Satisfactory yields of all four isomers of propiconazole were obtained by this method (Table 1); all gave satisfactory data for chemical, optical and radiochemical purity. The radiochemical

Table 1. Yield and purity of [triazole-3(5)-^{14}C]-propiconazole stereoisomers.

[Triazole-3(5)-^{14}C]-	R_f[a]	Yield[b] (%)	Radiochemical yield (%)[c,d]	Specific activity (mCi/mmole)[c]	Purity[e] (%)
2R, 4R (**1a**)	0.20	45	31	1.67	>98
2S, 4R (**1c**)	0.26	28	19	1.64	>99
2R, 4S (**1b**)	0.20	29	23	1.67	>99
2S, 4S (**1d**)	0.26	39	31	1.65	>98

[a] On silica gel 60 F_{254} developed with ethyl acetate:hexane (1:1, by volume).

[b] Based on bromomethyldioxolane (**3**).

[c] Determined by liquid scintillation counting.

[d] Based on [3(5)-^{14}C]-1,2,4-triazole.

[e] Determined by radio-TLC and NMR.

yields are lower than the chemical yields because an excess of [3(5)-^{14}C]-triazole was used, after trial studies with unlabelled material revealed that this led to greater purity of the desired products.

Compared with the published synthesis of propiconazole stereoisomers (2), the procedure described offers a number of advantages: it is suitable for small-scale work and does not involve hazardous purification steps (such as distillation of labelled compounds under reduced pressure); it could easily be adapted to the synthesis of similar molecules bearing radiolabel in other parts of the molecule. The method described should make propiconazole available for detailed investigation of its biochemical properties.

EXPERIMENTAL

Materials and Methods:

(R)-(+)-Pentane-1,2-diol (e.e. >98%, specific rotation +14.7°) and (S)-(-)-pentane-1,2-diol (e.e. >98%, specific rotation -15.8°) were gifts from Ciba-Geigy A.G. Their preparation has been described in the literature (2). [3(5)-^{14}C]1H-1,2,4-Triazole (specific activity 1.65 mCi/mM, radiochemical purity >98%) was obtained from ICI Chemicals and Polymers Ltd, Cleveland, U.K. All solvents were redistilled (dimethyl sulphoxide under reduced pressure); other reagents and materials were used without further purification. All reactions were performed under a positive pressure of nitrogen gas provided by a stopcock adaptor and a N_2-filled balloon. Analytical (0.25 mm layer thickness) and preparative TLC (2.0 mm layer thickness) was carried out using silica gel 60 F_{254} glass plates. Flash chromatography (5) was performed on silica gel 60 (particle size 0.040-0.063 mm). 400 MHz ^{1}H NMR spectra were obtained for samples in deuterochloroform, in 5 mm o.d. tubes, using tetramethylsilane as internal standard.

2-Bromo-2',4'-dichloroacetophenone (3):

Bromination of 2,4-dichloroacetophenone with bromine (0.5 equiv) in glacial acetic acid (4), followed by distillation under reduced pressure, gave a yellow oil, b.p. 155-170°/20 mmHg. Yield (based on Br_2): 90%. NMR indicated 95% purity; δ 7.56 (*d*, J = 8.3 Hz, 1H, H-6'), 7.48 (*d*,

J = 2.0 Hz, 1H, H-3'), 7.36 (*dd*, *J* = 2.0, 8.3 Hz, 1H, H-5'), 4.50 (*s*, 2H, H-2).

(4R)-2-Bromomethyl-2-(2',4'-dichlorophenyl)-4-propyl-1,3-dioxolane (4a and 4c):

A solution of 2-bromo-2',4'-dichloroacetophenone (6.7 g, 0.025 mole), (R)-(+)-pentane-1,2-diol (2.55 g, 0.025 mole) and 4-toluenesulphonic acid (0.25 g) in toluene (50 ml) was heated under reflux for 17 h, water being removed using a Dean and Stark separator. After cooling, the solution was diluted with diethyl ether (100 ml) and washed with water (2 x 100 ml), sodium bicarbonate solution (50 ml), water (100 ml) and saturated sodium chloride solution (75 ml), and dried over anhydrous sodium sulphate. After filtration and removal of solvents *in vacuo*, a dark yellow viscous oil was obtained (yield 8.4 g, 96%), which was purified by flash chromatography (5), eluting with ethyl acetate:hexane (1:1, by volume). Fractions containing material of R_f 0.46 (TLC on 10 x 3.5 cm silica gel plates, developed with benzene:hexane (1:1, by volume)) were combined and evaporated to give an orange viscous oil, which was shown by NMR to be >97% pure. NMR: δ 7.67 (*d*, *J* = 8.3 Hz) and 7.62 (*d*, *J* = 8.3 Hz), 1H, H-6'; 7.40 (*d*, *J* = 2.2 Hz, 1H, H-3'); 7.24 (*dd*, *J* = 2.2, 8.3 Hz, 1H, H-5'); 4.37-4.44 (*m*) and 4.28-4.32 (*m*), 1H, dioxolane H; 3.93-4.03 (*m*), 3.71-3.77 (*m*) and 3.40-3.46 (*m*), 2H, dioxolane H; 3.91 and 3.82 (AB*q*, *J* = 11.2 Hz) and 3.88 and 3.83 (AB*q*, *J* = 11.1 Hz), 2H, CH_AH_BBr; 1.24-1.86 (*m*, 4H, $CH_2CH_2CH_3$); 0.97 (*t*, *J* = 7.3 Hz) and 0.91 (*t*, *J* = 7.1 Hz), 3H, CH_3. The NMR spectrum indicated the diastereoisomer ratio to be 53:47.

[Triazole-3(5)-^{14}C]-(4R)-Propiconazole (1a and 1c):

A solution of [3(5)-^{14}C]-1,2,4-triazole (29 mg, 0.42 mmol; 0.69 mCi) in ethanol (0.2 ml) was placed in a one-piece flask/condenser assembly fitted with a side-arm, and the solvent evaporated off with a gentle stream of N_2. A small magnet and freshly powdered KOH (*ca.* 25 mg; excess) and dimethyl sulphoxide (1 ml) were quickly added via the side-arm, which was then closed with a "Suba-seal" stopper. Air inside the apparatus was replaced by N_2 and the mixture stirred at 45-50° (bath temperature) until all the KOH had dissolved (1 h). The temperature was then raised to

144°, and (4R)-bromomethyldioxolane (100 mg, 0.28 mmol) added over a period of 15 min. Stirring was continued at 144° for a further 18 h, during which time the reaction mixture became pale brown.

After cooling, the contents of the flask were transferred to a separating funnel, using cold water (2 x 2 ml) and diethyl ether (5 ml) to ensure quentitative transfer. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 5ml); the combined ether layers were washed with water (3 x 5ml) and saturated sodium chloride (5 ml). After evaporation of the solvent using a gentle stream of N_2, a dark orange oil was obtained; yield 95.5 mg (99%); radiochemical yield 70%. NMR spectroscopy indicated that the product was 83 % pure and that the diastereoisomeric ratio was 46:54.

[Triazole-3(5)-^{14}C]-(2R,4R)-propiconazole (1a) and [triazole-3(5)-^{14}C]-(2S,4R)-propiconazole (1c):

The crude (2RS, 4R)-[^{14}C]-propiconazole (95.5 mg), in dichloromethane (1 ml), was applied to a 20 x 20 cm preparative TLC plate, which was then developed four times with ethyl acetate:hexane (1:1, by volume), the plate being dried under a stream of N_2 after each development. Visualisation under UV light (254 nm) revealed two distinct bands, each of which was scraped off and extracted with acetone (40 ml). Slower band: **(2R, 4R)-[^{14}C]-Propiconazole (1a)**: R_f 0.20; NMR: δ 8.16 (*s*, 1H) and 7.89 (*s*, 1H), triazole H; 7.56 (*d*, J = 8.5 Hz, 1H, H-6′); 7.45 (*d*, J = 2.2 Hz, 1H, H-3′); 7.22 (*dd*, J = 2.2, 8.5 Hz, 1H, H-5′); 4.72 and 4.69 (AB*q*, J = 14.6 Hz), 2H, CH_AH_B-triazole; 3.96-4.00 (*dd*), 3.68-3.77 (*m*) and 3.34 (*t*, J = 8.3 Hz), 3H, dioxolane H; 1.2-1.6 (*m*, 4H, $CH_2CH_2CH_3$); 0.87 (*t*, J = 7.1 Hz, 3H, $CH_2CH_2CH_3$). Faster band: **(2S, 4R)-Propiconazole (1c)**: R_f: 0.26; NMR: δ 8.19 (*s*, 1H) and 7.90 (*s*, 1H), triazole H; 7.54 (*d*, J = 8.3 Hz, 1H, H-6′); 7.45 (*d*, J = 2.2 Hz, 1H, H-3′); 7.23 (*dd*, J = 2.2, 8.5 Hz, 1H, H-5′); 4.78 and 4.70 (AB*q*, J = 14.6 Hz), 2H, CH_AH_B-triazole; 3.87-3.95 (*m*) and 3.13-3.29 (*m*), 3H, dioxolane H; 1.2-1.5 (*m*, 4H, $CH_2CH_2CH_3$); 0.90 (*t*, J = 7.1 Hz, 3H, $CH_2CH_2CH_3$). For data on yields, radiochemical yields, specific activities and purity of compounds **1a** and **1c**, see Table 1.

[Triazole-3(5)-^{14}C]-(2R,4S)-Propiconazole (1b) and [triazole-3(5)-^{14}C]-(2S,4S)-propiconazole (1d):

(2RS, 4S)-2-Bromomethyl-2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolane(**4b** and **4d**) was prepared analogously to the (2RS, 4R)-compound (Section 2.3.), starting from (S)-(-)-pentane-1,2-diol; yield: 8.4 g (96%). After purification by flash chromatography, NMR indicated a purity of >97% and a diastereoisomer ratio of 50:50; remaining NMR data were identical to those of the (2RS, 4R) compound (section 2.3.). The purified (2RS, 4S) bromomethyldioxolane (117 mg; 0.33 mmole) was used to prepare (2RS, 4S)-[triazole-3(5)-^{14}C]-propiconazole (**1b** and **1d**) as described for the (2RS, 4R) isomers (Section 2.4.); yield: 114 mg (quantitative). The NMR spectrum indicated 83% purity and diastereoisomeric ratio 51:49. The separation of the diastereoisomers by preparative TLC was performed as described in Section 2.5. The R_f and NMR data of (2R,4S)- and (2S,4S)-propiconazole (**1b** and **1d** respectively) were identical to those of the corresponding (4R) isomers (Section 2.5.); for yield, radiochemical yield, specific activity and purity data, see Table 1.

ACKNOWLEDGEMENTS:

We thank Ciba-Geigy A.G. (Basle, Switzerland) for gifts of (R)- and (S)-pentane-1,2-diol, and the government of the Republic of Cyprus for financial support (to D. H.).

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