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STUDIES RELATED TO CEPHALOSPORINS. 6[1]. BROMINATION OF 3-EXOMETHYLENE IN CEPHAM DERIVATIVES

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Abstract : The methyl 3-methylene-7-phthalimidocepham-4-carboxylate 3, the corresponding (R)-oxide 2 and the 1,1-dioxide 1 add bromine affording stereoisomeric mixtures of dibromoderivatives. These results are at variance with previous reports regarding 3-exomethylene sulfides and sulfoxides. The stereochemistry of the dibromoderivatives was unambiguously determined via X ray crystallography of 5a, following ^{1}H-NMR correlations. The single dibromo derivatives, as well as the isomeric mixtures, can be dehydrobrominated to afford 3-bromomethyl cephem derivatives (7,8,9) in very good yields.

The addition of bromine to the 3-exomethylene cepham and the successive HBr elimination is probably one of the most straightforward routes to obtain 3-bromomethyl cephem. However, an unusual reactivity of the 3-exomethylene double bond has been reported in the case of cepham sulfides[2,3] and sulfoxides[3]. It has been claimed that these substrates do not add bromine under a variety of conditions, but, in the case of cepham sulfides[3], 3-bromomethyl cephems were directly obtained by the reaction of these substrates with bromine in the presence of a base (DBU). Speculations on this behavior have been put foreward.

Later Macchia and co-workers[4] succeded to carry out the same reaction with a bromine-lutidine complex.

Our interest in the substitution reaction at C-3' of the cephem nucleus[5] and the chemistry of cephem sulphones[6], prompted us to study the addition of bromine to the exomethylene sulfone 1.

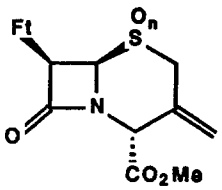
Sulfone 1 was obtained by oxidation with MCPBA of the (R) and (S)-methyl-3-methylene-7 β -phthalimido-cepham-4 α -carboxylate-1-oxide 2 the latter being obtained from the appropriate penam sulfoxide by the Kukoljia enlargment[7,1].

Compound 1 reacted in a few hours with an excess of bromine at 0°C in $CHCl_3$, affording two isomeric bromoderivatives 4. Separation by preparative HPLC of the mixture gave the isomers 4a and 4b in a ratio of 2:1. The α-configuration of the bromine at C-3 in the major isomer 4a was assigned on the basis of its spectroscopic properties and by correlation with the sulfoxide analogue, as it will be discussed subsequently.

Dehydrobromination of the mixture 4 with pyridine (or DBU) afforded 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate 1,1-dioxide 7 in a quantitative yield as crystalline material (m.p. 233-235°C). The bromide 7 was allowed to react with MeOH in the presence of $AgNO_3$ affording 3-methoxymethyl cephem derivative 10 in good yield.

In general, the sulfone 1 did not appear to us to be more reactive than the corresponding sulfide 3 in electrophilic additions[8] : therefore we tested the same bromine addition on sulfide 3 and sulfoxide 2 (R-isomer).

SCHEME



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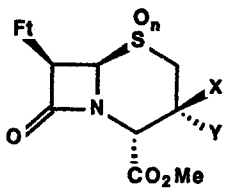
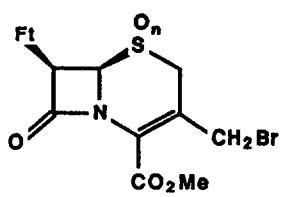
n* = 1 2
n = 0 3



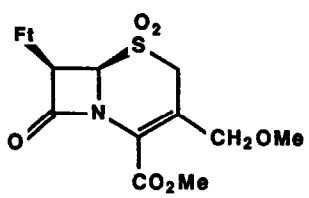
n = 2 4a X = CH_2Br, Y = Br 4b X = Br, Y = CH_2Br

n* = 1 5a X = CH_2Br, Y = Br 5b X = Br, Y = CH_2Br

n = 0 6a X = CH_2Br, Y = Br 6b X = Br, Y = CH_2Br



n* = 2 7
n* = 1 8
n = 0 9



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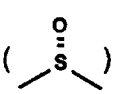
* R isomer ()

The sulfide was obtained by direct PBr_3 reduction of a mixture of (R) and (S)-sulfoxides 2.

In both cases we readily obtained the dibromoderivatives as isomeric mixtures in almost quantitative yields. The reaction was complete within 24 hours and no large excess of bromine was required in the case of sulfide 3. HPLC separation of the product mixtures gave 5a, 5b (sulfoxides) and 6a, 6b (sulfides) in ratios of 4:1 and 5:1 respectively.

Since spectral data did not allow the unambiguous determination of the structure of each isomer, 5a was submitted to X-ray crystallographyc studies; the results are shown in figure.

Interpretation of the ^{1}H-NMR spectra of all the dibromoderivatives was considerably simplified by the knowledge of the spectrum of compound 5a. The downfield shift (c.a. 0.44 p.p.m.) displayed by the CH_2-Br protons in the spectrum of the more abundant isomers 4a, 5a, 6a (of each couple), is probably due to a deshielding effect operated by the phthalimido group when the bromomethyl group is in the βconfiguration, consequently the stereochemistry of each compound arises as displayed in the structures (Scheme).

The spectroscopic correlation among the isomers is supported also by the chromatographic behaviour of the components of each couple: 4a, 5a, 6a are in fact less polar than 4b, 5b and 6b respectively.

Dehydrobromination of mixtures 5 and 6, with pyridine and DBU (-70°C) respectively, afforded sulfoxide 8 and sulfide 9. The latter was found to be identical to the product obtained from 3 according to the Koppel bromination procedure[3] (Br_2-DBU complex).

Sulfoxide 8 after PBr_3 reduction[9] gave a product identical to sulfide 9[10].

Some comments on the stereochemistry of the reaction (i.e. the preferential formation of 3 α-bromo derivatives) are due.

Since the substrates considered are methyl esters, a preferential electrophilic attack (in analogy with previous findings[11] and some more results in our hands[8]) should be considered. The successive nucleophilic attack is at C-3' (less hindered side), at variance of the Markovnicov rule: actually, ^{13}C resonances of C-3 and C-3' suggest very similar electron densities, whereas ^{13}C resonances of the two carbons of exocyclic olefins are in general quite different[12].

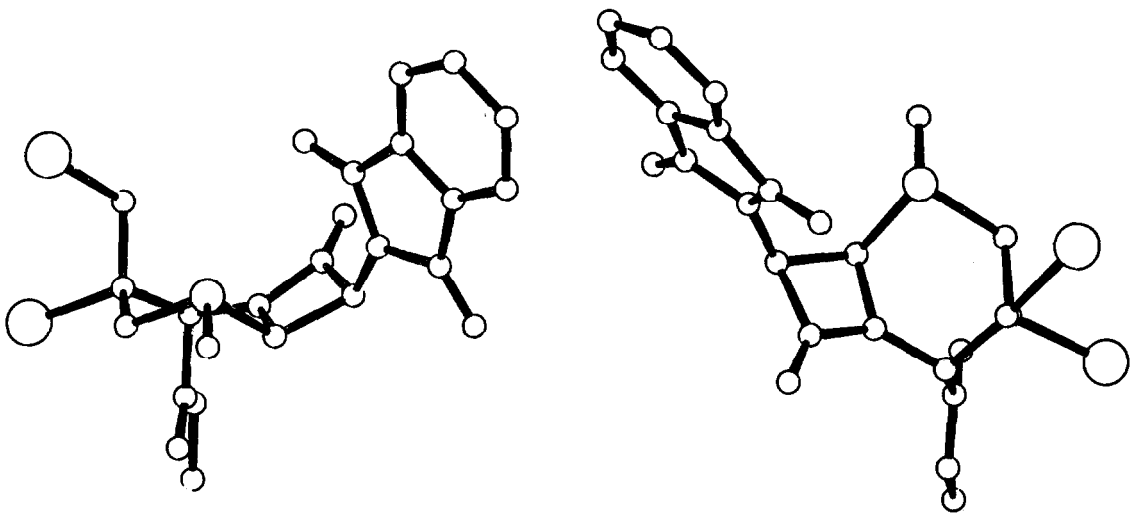
An alternative explanation is based on the possible high carbonium ion character at C-3 of the bromonium intermediate, since this electron deficient center can be assisted by sulfur and nitrogen atoms[13]. In this way the intermediate, in the case of sulfide and sulfoxide, suffers the nucleophilic attack through an S_N1-like process and 3 α-bromo derivatives are generated.

The lack of stabilization by the sulfur atom in the case of sulfone justifies the maximum amount of 3 β-bromo isomer obtained here.

Additional data based on MM2 energy calculations[14] show that for each couples (sulfides 6, sulfoxides 5, sulfones 4) the 3 α-bromo-3 β-bromomethyl derivatives 4a, 5a, 6a (major products) are also the most stable isomers (by more than 3 Kcal/mol).

The results indicate that the reactivity of 3-exomethylene cepham derivatives towards bromine is that expected for a double bond and the direction of attack is strongly dependent on the bulkiness of the ester group at C-4 and that, according to our results, is the reason for the different results recorded in the literature[3] on this argument.

FIGURE



The reaction described represents also an useful way to prepare 3-bromoethyl-3-cephem sulfides, sulfoxides and sulfones from a common precursor, easily available through the Kukoljia enlargement procedure of penicillin[7].

Experimental Part

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H-NMR were obtained on a Varian EM 360 A instrument and referred to tetramethylsilane as the internal standard. Electron-impact mass spectra were recorded at 70 eV on an AEI MS 12 spectrometer at a source temperature of 150-200°C. Elemental analyses were performed by ACRAF Research Laboratories, Roma.

Preparative and analytical TLC were performed on pre-coated Carlo Erba Stratocrom SiF_{254} plates. Column chromatographies were performed using pre-washed (2 N HCl followed by water) Merck Kieselgel 60 (70-230 mesh ASTM). HPLC separations were performed on a Water Associates instrument (model 6000 A) using a Water Associates column (Bondapak C 18) and a spectrophotometric detector Perkin-Elmer LC-55 B. Halogenated solvents were distilled from P_4O_{10}; anhydrous methanol was obtained by distillation from sodium metal; triethylamine and pyridine were distilled from KOH.

Bromination of Methyl 3-methylene-7-phthalimidocepham-4-carboxylate 1,1-dioxide 1 :

Methyl 3-methylene-7-phthalimidocepham-4-carboxylate 1,1-dioxide 1 (50 mg, 0.13 mmol) was dissolved in dry $CHCl_3$ (2.5 ml) and cooled to 0°C. Br_2 (0.1 ml) was added and the solution was stirred for 5 hr. Dilution with $CHCl_3$ and washing with an aqueous solution of $Na_2S_2O_5$ (10%), then with water followed by evaporation to dryness of the dried organic phases (Na_2SO_4), afforded the epimeric mixture of the dibromoderivatives 4a and 4b (yield 99%). HPLC ($CHCl_3$-EtOAc, 8:2) separation of the isomers gave pure 4a (46%) and 4b (24%). MS of the isomers were identical : m/z 484,486,488 (1:2:1) (M^+-SO_2).

Methyl 3 α -bromo-3 β -bromoethyl-7-phthalimidocepham-4-carboxylate 1,1-dioxide 4a : IR ($CHCl_3$): ν max = 1805 (β-lactam), 1730 (ester + imide), 1305, 1140 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) : δ = 7.40-7.90 (m,4H,phthalimido), 5.60 (d,1H, J=4Hz,C_7-H), 5.15 (d,1H, J=4Hz,C_6-H), 5.05 (s,1H,C_4-H), 4.30 (s,2H,C_3'-H), 4.30 and 3.80 (AB system,2H,J=14Hz,C_2-H), 3.75 ppm (s,3H,CO_2CH_3). Elemental analysis: found C:37.34%, H:2.65%, N:4.87%; calc.: for $C_{17}H_{14}N_2O_7SBr_2$ C:37.11%, H:2.56%, N:5.09%.

Methyl 3 α -bromomethyl-3 β -bromo-7-phthalimido-4-carboxylate 1,1-dioxide 4b: IR ($CHCl_3$) : ν max = 1805 (β-lactam), 1730 (ester + imide), 1350-1140 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$) δ = 7.40-7.90 (m,4H,phthalimido), 5.65 (d,1H, J=4Hz,C_7-H), 5.10 (d,2H, J=4Hz,C_6-H+C_4-H), 4.02 and 3.50 (AB system, 2H,J=16Hz,C_2-H), 3.80 ppm (s,5H,C_3,-H + CO_2CH_3).

Methyl 3-bromomethyl-7-phthalimido-3-cefem-4-carboxylate 1,1-dioxide 7 :

The dibromoderivatives mixture 4a-b (50 mg, 0.09 mmol) was dissolved in dry $CHCl_3$ (3.5 ml) and dry THF (0.1 ml) and cooled to -70°C. A solution (46 l) of DBU in $CHCl_3$ (15%) was added at this temperature and the resulting solution was stirred for 2 hr. 10^{-1} M HCl (0.4 ml) was added and the temperature was allowed to rise to room temperature. Dilution with $CHCl_3$, washing with H_2O and brine followed by evaporation of the dried (Na_2SO_4) solvents gave 7 (48 mg, 99%) chromatographically pure (HPLC). m.p. 233-5°C dec. (MeOH). MS: m/z = 404, 406 (1:1) (M^+-SO_2). IR ($CHCl_3$) ν max = 1820 (β-lactam), 1725 (ester + imide), 1350 and 1130 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$): δ = 7.45-7.90 (m,4H,phthalimido), 6.85 (d,1H, J=4Hz,C_7-H), 4.4-4.75 (m,4H,C_6-H+C_3,-H+C_2-H), 3.85 (s,3H,CO_2CH_3), 3.6-3.85 ppm (d,1H, J=5Hz,C_2-H).
Elemental analysis: found C:43.11%, H:2.68%, N:5.72%; calc. for $C_{17}H_{13}N_2O_7SBr$ C:43.51%, H:2.79%, N:5.97%.

Methyl 3-methoxymethyl-7-phthalimido-3-cefem-4-carboxylate 1,1-dioxide 10 :

To a solution of methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate 1,1-dioxide 7 (50 mg, 0.11 mmol) in dry MeOH (20 ml), $AgNO_3$ (20 mg, 0.12 mmol) was added and the mixture was stirred at room temperature in the dark for 30'.
Filtration on a small celite column eluting with $CHCl_3$ followed by washing the solution with H_2O and evaporation of the dried solvents (Na_2SO_4) to dryness gave the methyl 3-methoxymethyl-7-phthalimido-3-cephem-4-carboxylate 1,1-dioxide 10 (42.5 mg; 94%) pure. MS: m/z = 420 (M^+). IR ($CHCl_3$) : ν max = 1800 (β-lactam), 1720 (ester + imide), 1330 and 1120 cm^{-1} (SO_2). ^{1}H-NMR ($CDCl_3$): δ = 7.40-7.90 (m,4H,phthalimide), 5.85 (d,1H, J=4Hz,C_7-H), 4.55 (s,2H,C_3'-H), 4.52 (d,1H, J=4Hz,C_6-H), 3.85 (s,3H,CO_2CH_3), 4.35 and 3.75 (AB system,2H,J=14Hz,C_2-H), 3.35 ppm (s,3H,OCH_3).

Bromination of Methyl 3-methylene-7-phthalimidocepham-4-carboxylate 3 :

Compound 3 (80 mg, 0.22 mmol) dissolved in dry $CHCl_3$ and 0.24 ml of a 10% (v/v) solution of Br_2 in $CHCl_3$ was added. After 8 hr the reaction was completed (TLC, $CHCl_3$-EtOAc 8:2) and the solution was diluted with $CHCl_3$ and washed with an aqueous solution (10%) of $Na_2S_2O_5$ followed by saturated aqueous solution of $NaHCO_3$ and then with H_2O. Evaporation of the dried (Na_2SO_4) solvents gave 115 mg (quantitative yield) of a 5:1 mixture of 6a and 6b. HPLC separation of the epimers ($CHCl_3$-EtOAc 8:2) afforded 88 mg of 6a (77%) and 16 mg of 6b (14%). Ms of the isomers were identical : m/z = 516, 518, 520 (1:2:1) (M^+).

Methyl 3 α -bromo-3 β -bromomethyl-7-phthalimidocepham-4-carboxylate 6a : Foam. IR ($CHCl_3$) : ν max = 1780 (β-lactam), 1725 cm^{-1} (ester + imide). ^{1}H-NMR ($CDCl_3$) : δ = 7.55-7.9 (m,4H,phthalimido), 5.50 (d,1H, J=4Hz, C_7-H), 5.43 (d,1H, J=4Hz, C_6-H), 5.0 (s,1H,C_4-H), 4.72 and 4.18 (AB system,2H,J=11Hz,C_3'-H), 4.15 and 3.30 (AB system,2H,J=13Hz,C_2-H), 3.80 ppm (s,3H,CO_2CH_3).
Elemental analysis : found C:39.37%, H:2.78%, N:5.35%; calc. for $C_{17}H_{14}N_2O_5SBr_2$, C:39.40%, H:2.72%, N:5.40%.

Methyl 3 α -bromomethyl-3 β -bromo-7-phthalimidocepham-4-carboxylate 6b : mp 118-121°C dec. (benzene-hexane). IR (KBr) : ν max = 1780 (β-lactam), 1725 cm^{-1} (ester + imide). ^{1}H-NMR ($CDCl_3$) : δ = 7.6-7.9 (m,4H,phthalimido), 5.55 (d,1H, J=4Hz, C_7-H), 5.25 (d,1H, J=4Hz, C_6-H), 5.22 (s,1H,C_4-H), 4.10 and 3.82 (AB system,2H,J=12Hz,C_3'-H), 3.80 (s,3H,CO_2CH_3), 3.60 and 3.26 ppm (AB system,2H,J=12Hz,C_2-H).

Methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate 9 :

56 mg (0.11mmol) of the epimeric mixture of 6a and 6b were dissolved in 5 ml of a $CHCl_3$-THF solution (4:1) and cooled to -65°C (dry ice-$CHCl_3$ bath). A 10% (v/v) solution of DBU in anhydrous $CHCl_3$ (eq.DBU/eq 6 = 1) was added and the resulting solution was left 100 min under stirring. The reaction was quenched by adding 10^{-2} M HCl (0.3 ml) and the temperature was allowed to raise up to room temperature.
Separation of the organic layer, washing with H_2O and evaporation of the dried solvents afforded methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate 9 (45 mg, 95% yield) chromatographically pure. The identity of 9 was proved by comparison with an authentic sample prepared via a different route[5].

Bromination of (R)-methyl 3-methylene-7-phthalimidocepham-4-carboxylate 1-oxide 2 :

(R)-Methyl-3-methylene-7-phthalimidocepham-4-carboxylate 1-oxide 2 (60 mg, 0.16 mmol) was dissolved in dry $CHCl_3$ (3 ml) and after cooling to 15°C, Br_2 (0.12 ml) was added. The reaction was left (24 hr) until no more starting material was detected (HPLC, EtOAc as solvent). The solution was diluted with $CHCl_3$ and washed with an aqueous solution (10%) of $Na_2S_2O_5$, then with a saturated aqueous solution of $NaHCO_3$ followed by H_2O. Evaporation of dried solvents gave 86 mg (quantitative yield) of a 4:1 mixture of 5a and 5b (on the basis of HPLC analysis). HPLC separation afforded 5a (46 mg) and 5b (12 mg) as pure foams. MS of the isomers were identical : m/z = 484, 486, 488 (1:2:1) (M^+-SO).

(R)-Methyl 3 α -bromo-3 β -bromomethyl-7-phthalimidocepham-4-carboxylate 1-oxide 5a: mp 230-2°C dec. (CH_2Cl_2-CH_3CN). IR (KBr) : ν max = 1800 (β-lactam), 1730 cm^{-1} (ester + imide). ^{1}H-NMR ($CDCl_3$) : δ = 7.55-7.95 (m,4H,phthalimido), 5.78 (d,1H, J=4Hz, C_7-H), 5.09 (d,1H, J=4Hz,C_6-H), 4.88 (s,1H,C_4-H), 4.30 and 4.10 (AB system,2H,J=12.9,C_2-H), 3.85 ppm (s,3H,CO_2CH_3).

(R)-Methyl 3 α -bromomethyl-3 β -bromo-7-phthalimidocepham-4-carboxylate 1-oxide 5b : IR ($CHCl_3$): ν max = 1800 (β-lactam), 1730 cm^{-1} (ester + imide). ^{1}H-NMR ($CDCl_3$): δ = 7.7-7.98 (m,4H,phthalimido), 5.93 (d,1H, J=4Hz,C_7-H), 5.05 (d,1H, J=4Hz,C_6-H), 4.98 (s,1H,C_4-H), 4.1 and 3.7 (AB system,2H,J=18Hz,C_2-H), 3.88 (s,3H,CO_2CH_3), 3.83 ppm (s,2H,C_3'-H). Elemental analysis : found C:39.38%, H:2.59%, N:5.19%; calc. for $C_{17}H_{14}N_2O_6SBr_2$ C:38.22%, H:2.64%, N:5.24%.

(R)-Methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate 1-oxide 8 :

The epimeric mixture 5 (68 mg, 0.13 mmol) was dissolvedin $CHCl_3$ (5 ml), distilled pyridine (24 1) was added and the solution was left 24 hr at room temperature (the reaction was followed by HPLC using EtOAc as solvent). The solution was washed with 10^{-2}M HCl, H_2O and dried over Na_2SO_4. Evaporation of the solvents to dryness gave (R)-methyl-3-bromomethyl-3-cephem-4-carboxylate 1-oxide 8 (50 mg, 80%) as a foam chromatographically pure. MS : m/z = 452, 454 (M^+). IR ($CHCl_3$) : ν max = 1800 (β-lactam), 1730 cm^{-1} (ester + imide). ^{1}H-NMR ($CDCl_3$) :δ = 7.47-7.83 (m,4H,phthalimido), 5.93 (d,1H, J=5Hz,C_7-H), 4.63 (d,1H, J=5Hz, C_6-H), 4.43 (s,2H,C_3'-H), 4.14 and 3.64 (AB system,2H,J=15Hz,C_2-H), 3.83 ppm (s,3H,CO_2CH_3). Elemental analysis : found C:44.98%, H:2.91%, N:6.15%; calc. for $C_{17}H_{13}N_2O_6SBr$ C:45.04%, H:2.89%, N:6.18.

Reduction of (R)-methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate-1-oxide 8:

Compound 8 (50 mg, 0.11 mmol) was dissolved in freshly distilled DMF (0.6 ml), the solution was cooled to 0°C and PBr_3 (10 1) was added. After 2 hr the reaction was finished and saturated aqueous solution of $NaHCO_3$ (2 ml) was added. The mixture was extracted (x3) with $CHCl_3$ and the combined organic extracts were dried with Na_2SO_4. Evaporation of the solvents to dryness gave (42 mg, 87%) chromatographically pure. The identity of 9 was proved by comparison with an authentic sample prepared via a different route[5].

X-Ray Analysis of (R)-Methyl 3 α -bromo-3 β -bromomethyl-7-phthalimidocepham-4-carboxylate 1-oxide 5a :

Crystal data are $C_{17}H_{14}N_2O_6SBr_2$, M=534.19, monoclinic, a=6.972(6), b=15.071(9), c=9.198(18) Å, β=97.54(13)°, V=958.1 Å^3, space group $P2_1$, Z=2, D_x=1.85 gmc^{-3}, F(000)=528, Mokα(λ=71069), μ=42.59 cm^{-1}.
The intensity data of 3585 independent reflections, 2834 of which with $I \geq 3\ (I)$, were collected on an automatic four-circle diffractometer, using monochromatized Mokα radiation, ω-scan mode, from a crystal of 0.5x0.5x0.25 mm, up to a 2θ value of 65°.
No correction for absorption or extinction was applied. The crystal structure was solved by MULTAN 80[15] and DIRDIF[16] and refined by full matrix least squares method[17].
The refinement of all the non-H atoms, using anisotropic thermal parameters, led to an R=0.067.
A final difference Fourier synthesis showed no peaks >1.9 e Å^{-3}.

Acknowledgments

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