The Preparation and Reactions of 2-Benzyloxy-4-benzylideneoxazol-5-one

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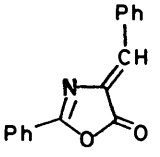
The preparation of the title compound (4) and a survey of its chemistry are described. Its reactivity towards nucleophiles at C-5 is high compared with that of the corresponding 2-phenyl compound (1), and nucleophilic reagents attack (4) exclusively at this position, in contrast to the behaviour of (1).

2-ALKYL- and 2-ARYL-4-ALKYLIDENEOXAZOL-5-ONES, especially benzylidene derivatives such as (1), have been widely investigated ever since the classic work of Erlenmeyer.[1] Their principal importance is in connection with amino-acid synthesis: the alkylidene group can be elaborated in various useful ways to give saturated oxazol-5(4*H*)-ones which yield acylamino-acids on mild hydrolysis.[2] The fact that nucleophilic ring opening of the 4-alkylideneoxazol-5-ones themselves gives αβ-unsaturated α-amino-acid derivatives (*i.e.* dehydroamino-acid derivatives) has added to their interest in recent years.[3]

We have recently proved the structure of and described a novel class of oxazol-5(4*H*)-ones (2) derived from benzyloxycarbonylamino-acids.[4] The 2-benzyloxy-compounds (2) are more easily attacked by nucleophiles at position 5 and less easily ionised at position 4 than are the well known 2-alkyl- and 2-aryl-oxazol-5(4*H*)-ones (3). We now report the preparation of the corresponding 4-benzylideneoxazol-5-one (4) and a survey of its reactions.

Attempted Erlenmeyer-type reactions between benzyloxycarbonylglycine or the corresponding unstable oxazol-5(4*H*)-one and benzaldehyde gave intractable mixtures (*cf.* ref. 5), but treatment of benzyloxycarbonyl-*threo*-β-phenylserine with phosphorus pentachloride at low temperatures followed by addition of triethylamine gave (4) as a single stereoisomer in fair yield. Benzyloxycarbonyl-*erythro*-β-phenylserine gave the same product in lower yield. In neither case was any of the stereoisomeric unsaturated oxazol-5-one detected in the crude mixtures. That the stereochemistry is *Z* follows from the coupling constant of 3.7 ± 1.2 Hz between the vinylic proton and carboxy-carbon observed in the ^{13}C n.m.r. spectrum of the benzyloxycarbonyldehydrophenylalanine produced on hydrolytic ring-opening of (4): Prokof'ev and Karpeiskaya [6] have recently reported that in a series of (*Z*)-4-benzylideneoxazol-5-ones and the products of their hydrolysis, the $^3J_{H\beta,CO}$ values were all *ca.* 5.5 Hz but the values found for the *E*-isomers were *ca.* 12.5 Hz.

Treatment of the saturated oxazol-5(4*H*)-one (2; R = $PhCH_2$) with bromine–triethylamine gave a good yield of (4) but several other methods of oxidising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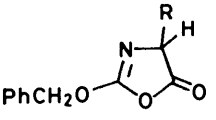
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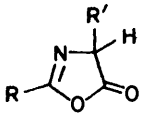
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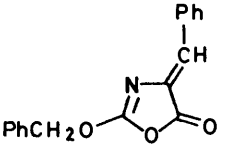
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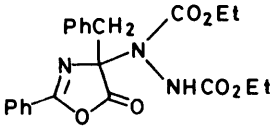
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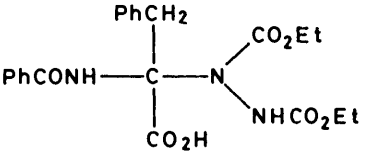
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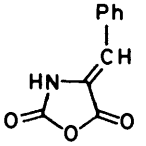
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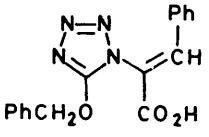
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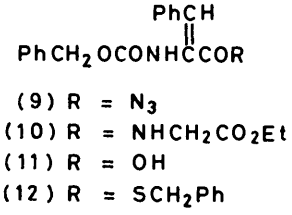
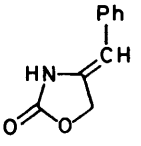

(9) R = N_3
(10) R = $NHCH_2CO_2Et$
(11) R = OH
(12) R = SCH_2Ph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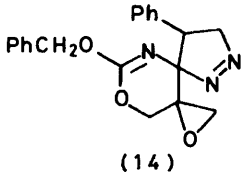
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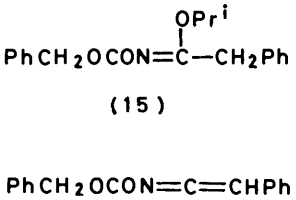
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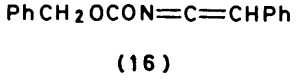
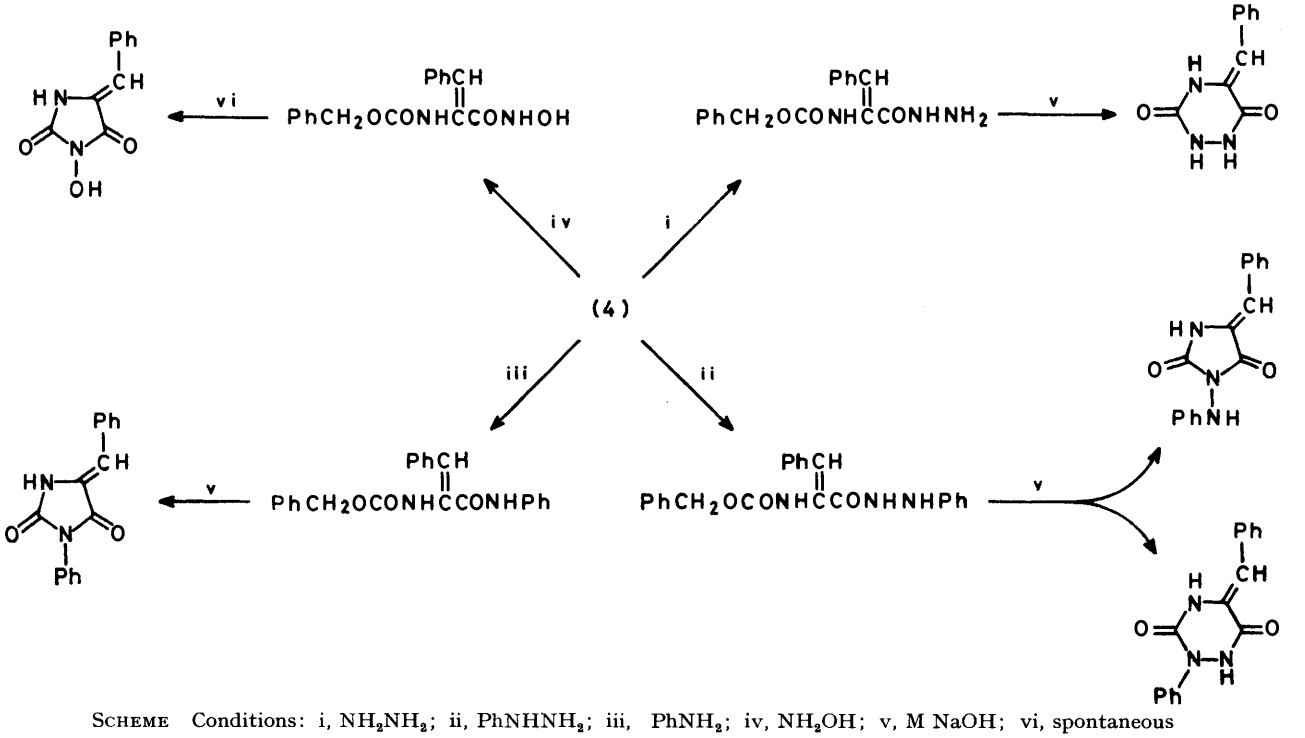

(16)

oxazol-5(4*H*)-ones which have been described previously gave only low yields or complex mixtures (see Experimental section). A novel means of oxidising oxazol-5(4*H*)-ones, treatment with triethylamine and diethyl azodicarboxylate, which is exemplified here for the first time by a preparation of (1) from (3; R′ = $PhCH_2$, R = Ph) was also unsatisfactory for the conversion of (2; R = $PhCH_2$) into (4). This oxidation of (3) probably proceeds by addition of the oxazol-5(4*H*)-one anion to the reagent giving (5) which then ejects bis-ethoxycarbonylhydrazine by β-elimination. The open-chain acid (6) corresponding to (5) was isolated (and characterised as its dicyclohexylammonium salt) on room temperature. Grignard reagents gave the αβ-unsaturated tertiary alcohols formed by attack at C-5 as the only isolable products, in contrast to the result [8] with (1) to which addition occurs in the side-chain. Lithium aluminium hydride treatment yielded (13), presumably by cyclisation of the initial product formed on reduction at C-5. Similar cyclisations occurred with ease on alkaline treatment of the derivatives of (4) obtained by reaction with aniline, hydrazine, phenylhydrazine, or hydroxylamine, providing simple routes to a variety of unusual heterocyclic compounds (see Scheme).

Treatment of (4) with diazomethane in ether gave the



SCHEME Conditions: i, NH_2NH_2; ii, $PhNHNH_2$; iii, $PhNH_2$; iv, NH_2OH; v, M NaOH; vi, spontaneous

hydrolytic work-up after treatment of (4) with diethyl azodicarboxylate without additional base.

Hydrogen chloride in chloroform converted (4) into the corresponding *N*-carboxyanhydride (7) in high yield: (7) was also formed by reaction with dimethyl sulphoxide, slowly at room temperature but rapidly on warming. Hydrazoic acid in chloroform gave substantial amounts of the tetrazole (8) analogous to the product obtained [7] by treating (1) with hydrazoic acid, but in the reaction with (4) the oily azide (9) was the major product. The spectroscopic characterisation of this relatively stable acyl azide was corroborated by treatment with glycine ethyl ester, which gave the dipeptide (10). The high reactivity of (4) towards nucleophiles at C-5 compared to that in (1) was a general feature of its chemistry. Sodium hydroxide under mild conditions gave the acid (11), glycine ethyl ester the dipeptide (10), and toluenethiol the thioester (12), although reaction with methanol in chloroform was very slow at tricyclic product (14) exactly analogous to that given [9] by the corresponding 2-benzylthiothiazol-5-one. We did not detect 1 : 1 adduct formation, which might have given access to some useful cyclopropylamino-acid derivatives, under any conditions. Photolysis of (4) in propan-2-ol proceeded quantitatively to give (15), presumably *via* (16), a pathway which was not observed [10] on irradiation of (1).

A number of other 4-alkylidene-2-benzyloxyoxazol-5-ones have been prepared and investigated: their chemistry is similar to that outlined for (4).[11] These compounds appear to be of some interest as intermediates for the preparation of benzyloxycarbonyldehydroamino-acid derivatives, which are, however, of strictly limited use for further synthetic elaboration as the enamines obtained on deprotection are very poor nucleophiles.[12] At the outset of the investigation we were attracted by the prospect of developing a useful general approach to unusual benzyloxycarbonylamino-acids based on side-

chain modification in structures such as (4) followed by hydrolytic ring-opening. This would appear to be precluded by the finding that all the nucleophilic reagents examined attack (4) almost exclusively at C-5, in contrast to the outcome with (1). 2-Alkoxy-4-alkylideneoxazol-5-ones may nevertheless be of some value, in heterocyclic syntheses of the kind shown in the Scheme.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded with tetramethylsilane as internal standard (a) for protons, with a Perkin-Elmer R32 spectrometer operating at 90 MHz and 310.5 K and (b) for carbon-13, on a Brüker WH90 instrument operating at 22.6 MHz and 305 K (assignments were confirmed by observation of C–H coupling but only the completely proton-decoupled spectra are reported). Electron impact (EI) mass spectra were recorded on a Varian CH7 spectrometer operating at 70 eV; chemical ionisation (CI) mass spectra were recorded on a Micromass 16F spectrometer. I.r. spectra were recorded on a Perkin-Elmer 297 grating spectrometer. U.v. spectra were recorded on a Cary 14 spectrometer. All the compounds described were chromatographically homogeneous and had i.r. spectra (and, where appropriate, u.v. spectra) in accord with the structures assigned but full data are only reported in selected cases.

(*Z*)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one*.—*Method A*. Phosphorus pentachloride (5.0 g, 24 mmol) was added to a stirred solution of *N*-benzyloxycarbonyl-DL-*threo*-β-phenylserine [13] (3.15 g, 10 mmol) in THF (5 ml) and ether (20 ml) at −20°. After 15 min the solution was filtered directly into a solution of triethylamine (15 ml, 107 mmol) in ether (100 ml) at −78°. After 5 min shaking, the cooling bath was removed and shaking was continued for a further 10 min. The mixture was then washed with M-hydrochloric acid and saturated sodium hydrogencarbonate, and dried. Evaporation gave a greenish solid which was triturated with two portions (8 ml) of ether, to give the required product as a pale green solid (1.35 g, 48%), which was generally used without further purification. Recrystallisation from ethyl acetate–light petroleum gave *unsaturated oxazolone* as pale green crystals, m.p. 138—139°; $\nu_{max.}$ 1 820, 1 795, and 1 670 cm^{-1}; δ([$^2H_6$]DMSO) 8.12 (2 H, m, ArH), 7.45 (8 H, m, ArH), 7.1 (1 H, m, CH:C), and 5.6 (2 H, s, $PhCH_2$); $\lambda_{max.}$ ($CHCl_3$) 331.5 (ε 33 750), 345 (25 150), 240 (6 345), and 234.5 nm (8 185); *m/e* (EI) 279 ($M^{\cdot+}$) (Found: C, 72.9; H, 4.6; N, 5.1. $C_{17}H_{13}NO_3$ requires C, 73.2; H ,4.7; N, 5.0%). The same unsaturated oxazolone (0.15 g, 27%) was obtained from *N*-benzyloxycarbonyl-DL-*erythro*-β-phenylserine [13] (0.63 g, 2 mmol) by the same procedure: in neither case was there any indication of the formation of the *E*-isomer.

Method B. Bromine (0.53 g, 3.33 mmol) was added to a stirred solution of 2-benzyloxy-4-benzyl-DL-oxazol-5(4*H*)-one (0.94 g, 3.33 mmol) and triethylamine (1.4 ml, 10 mmol) in deuteriochloroform (15 ml) at −30°. After 15 min n.m.r. showed no saturated oxazolone remaining, and the solution was washed with M-hydrochloric acid, saturated sodium hydrogencarbonate, and dried. Evaporation and trituration with ether (2 × 10 ml), gave *unsaturated oxazolone* (0.72 g, 77%), identical with that prepared by method A above. Dehydrogenation of 2-benzyloxy-4-benzyl-DL-oxazol-5(4*H*)-one could also be achieved, in lower yield, by treatment with sulphuryl chloride–triethylamine (*cf.* ref. 14) and some unsaturated oxazolone was produced with diethyl azodicarboxylate–triethylamine (*cf.* the case described below) but high potential quinones (*cf.* ref. 15) gave complex mixtures.

Reaction of 2-*Phenyl*-4-*benzyl*-L-*oxazol*-5(4H)-*one with Diethyl Azodicarboxylate*.—*A. Without added base*. A solution of 4-benzyl-2-phenyl-L-oxazol-5(4*H*)-one (0.61 g, 2.43 mmol) and diethyl azodicarboxylate (0.423 g, 2.43 mmol) in chloroform was stirred at 50—55° for 3 h. Evaporation gave a yellow oil which, after trituration with light petroleum, was partitioned between saturated sodium hydrogencarbonate and ether. The aqueous phase was acidified with M-hydrochloric acid, and extracted with ether. The ethereal extract was dried and evaporated to give *N-benzoyl*-DL-α-(NN′-*bisethoxycarbonylhydrazino*)*phenylalanine* as a crisp foam (0.6 g, 56%), $\delta_H(CDCl_3)$ 7.65 (2 H, m, ArH), 7.1—7.4 (10 H, m, ArH + 2 × N–H), 4.25 (2 H, qt, CH_3CH_2O), 3.68 (2 H, qt, CH_3CH_2O), 3.5 (2 H, m, $PhCH_2$), 1.27 (3 H, t, CH_3C), 0.88 (3 H, t, CH_3C); $\delta_C(CDCl_3)$ 171.7 (CO_2H), 159.8 (Ph*C*O), 155.0 and 151.5 (2 × CO_2Et), 133.8—126.9 (aryl carbons), 93.1 ($PhCH_2C$), 63.4 and 63.1 (2 × CH_3CH_2), 40.8 ($PhCH_2$), and 14.2 and 13.4 (2 × CH_3CH_2) p.p.m. The corresponding *acylamino-acid dicyclohexylammonium salt*, prepared in the usual way, had m.p. 188—189° (Found: C, 65.75; H, 7.5; N, 9.1. $C_{34}H_{18}N_4O_7$ requires C, 65.4; H, 7.7; N, 9.0%).

B. With added triethylamine. Triethylamine (0.56 ml, 4 mmol) and diethyl azodicarboxylate (0.69 g, 4 mmol) were added to a stirred solution of 2-phenyl-4-benzyl-L-oxazol-5(4*H*)-one (1.0 g, 4 mmol) in chloroform (15 ml) at 0°. After 10 min the cooling-bath was removed and stirring was continued for a further 18 h. Evaporation and trituration with ether gave (*Z*)-2-*phenyl*-4-*benzylideneoxazol*-5-*one* (0.68 g, 68%), m.p. 165—166° (lit.,[16] 166—167°), which was identical in every respect with an authentic specimen.

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Dimethyl Sulphoxide*.—N.m.r. investigation of a solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one in hexadeuteriodimethyl sulphoxide showed that there was a slow reaction on standing at room temperature. Reaction proceeded more rapidly on warming, being complete in 3 h at 70°, giving a mixture of dimethyl sulphide, benzaldehyde, and (*Z*)-4-benzylideneoxazolidine-2,5-dione.

Investigation of the Stability of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one towards Methanol*.—A solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.28 h, 1 mmol) in chloroform (2.5 ml) and methanol (1.0 ml) was stirred for 24 h. Evaporation of solvents gave unchanged *oxazolone* (0.28 g). No reaction was detected by either t.l.c. or n.m.r. investigations.

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Hydrogen Chloride*.—Hydrogen chloride gas was bubbled through a stirred solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.43 g, 1.54 mmol) in chloroform (10 ml) at 0°. A precipitate formed almost immediately. After 15 min, evaporation, trituration with ether, and washing with chloroform gave (*Z*)-4-benzylideneoxazolidine-2,5-dione (0.24 g, 83%), m.p. 230° (decomp.); $\nu_{max.}$ (Nujol) 1 825, 1 825, 1 760, and 1 655 cm^{-1}; δ_H([$^2H_6$]DMSO) 11.65br (1 H, s, NH), 7.7—7.35 (5 H, m, ArH), and 6.67 (1 H, s, PhCH:C); δ_C([$^2H_6$]DMSO) 162.1 (C·*C*O·O), 150.9 (N·CO·O), 132.0—123.8 (aryl carbons), 123.9 C:*C*·N), and 113.4 p.p.m. (Ph*C*H:C); $\lambda_{max.}$ (EtOH) 313 (ε 21 510), 235 (6 290), and

227.5 nm (6 295); *m/e* (CI) 190 (M + 1) (Found: C, 63.1; H, 3.55; N, 7.3. $C_{10}H_7NO_3$ requires C, 63.5; H, 3.7; N, 7.4%).

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Hydrazoic Acid.*—2-Benzyloxy-4-benzylideneoxazol-5-one (1.25 g, 4.5 mmol) was added to a stirred solution of hydrazoic acid in chloroform (1.25M, 6 ml) at 0°. After 10 min the cooling bath was removed and stirring was continued for a further 22 h. Evaporation gave an oil which was partitioned between ethyl acetate and saturated sodium hydrogencarbonate. The organic layer was dried and evaporated to give (Z)-N-*benzyloxycarbonyldehydrophenylalanine azide* (0.73 g, 50%) as a chromatographically homogeneous oil; $\nu_{max.}$ ($CDCl_3$) 2 150, 1 725, 1 675, and 1 640 cm^{-1}; δ($CDCl_3$) 7.6—7.1 (12 H, m, ArH + NH + PhCH:C) and 5.1 (2 H, s, $PhCH_2$); *m/e* (EI) 322 ($M^{+\cdot}$).

Acidification of the aqueous layer obtained above to pH 1 with 6M-hydrochloric acid gave an oil, which was extracted into chloroform. The organic phase was dried and evaporated giving 1-(5-*benzyloxytetrazol*-1-*yl*)*cinnamic acid* (0.57 g, 39%) as a solid. Recrystallisation from ethyl acetate–light petroleum gave the *tetrazole* as crystals, m.p. 120—121° (decomp.); δ($CDCl_3$) 9.7br (1 H, s, OH), 8.1 (1 H, s, PhCH:C), 7.5—6.9 (10 H, m, ArH), and 5.41 (2 H, m, $PhCH_2$) (Found: C, 61.7; H, 4.5; N, 17.0. $C_{17}H_{14}N_4O_3$,0.5H_2O requires C, 61.6; H, 4.5; N, 16.9%).

Reaction of (Z)-N$^{\alpha}$-*benzyloxycarbonyldehydrophenylalanine Azide with Glycine Ethyl Ester.*—A solution of (*Z*)-*N*-benzyloxycarbonyldehydrophenylalanine azide (0.29 g, 0.9 mmol), glycine ethyl ester hydrochloride (0.125 g, 0.9 mmol), and triethylamine (0.126 ml, 0.9 mmol) in chloroform (5 ml) was stirred for 72 h at room temperature. The mixture was washed with M-hydrochloric acid, dried, and evaporated to give an oily solid. Trituration with a small volume of ether and recrystallisation from dichloromethane–light petroleum gave (Z)-N-*benzyloxycarbonyldehydrophenylalanylglycine ethyl ester* (0.22 g, 65%), m.p. 125—126°, identical in every way with samples of this compound made by other routes.

(Z)-N-*Benzyloxycarbonyldehydrophenylalanine* [(Z)-2-*Benzyloxycarbonylaminocinnamic Acid*].—Sodium hydroxide (2M, 15 ml) was added to a stirred solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.93 g, 3.33 mmol) in THF (7.5 ml). After 1.25 h THF was removed and the residue was acidified to pH 1 with 5M-hydrochloric acid and extracted with ethyl acetate. The organic phase was dried and evaporated to give a creamy solid which was recrystallised from ethyl acetate–light petroleum giving *acyldehydroamino-acid* as needles (0.6 g, 61%), m.p. 156—158°, δ(CD_3OD) 7.65—7.5 (2 H, m, ArH), 7.45 (1 H, s, PhCH:C), 7.3 (8 H, m, ArH), and 5.1 (2 H, s, $PhCH_2$) $\lambda_{max.}$ (EtOH) 280 nm (ε 19 000); *m/e* (CI) 298 (M + 1) (Found: C, 68.5; H, 5.1; N, 4.8. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); δ_C(CD_3OD) 171.0 (d, $^3J_{H\beta.CO}$ 3.7 ± 1.2 Hz).

N-*Benzyloxycarbonyl*-(Z)-*dehydrophenylalanylglycine Ethyl Ester.*—Glycine ethyl ester hydrochloride (0.44 g, 3.17 mmol) was added to a stirred solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.8 g, 2.87 mmol) and triethylamine (0.47 ml, 3.35 mmol) in THF (10 ml) at 0°. After 0.5 h, the cooling bath was removed, and stirring was continued for a further 6 h. Evaporation gave an oily solid, which was partitioned between ethyl acetate and M-hydrochloric acid. The organic layer was dried and evaporated to give an oil which was triturated with ether (2 × 4 ml), giving a chromatographically homogeneous solid (0.73 g, 67%). Recrystallisation from chloroform–light petroleum gave an analytical sample of *dipeptide ester* as needles, m.p. 125—126°; δ($CDCl_3$) 7.25 (10 H, m, ArH), 7.15 (1 H, s, PhCH:C), 4.13 (2 H, qt, CH_2CH_3), 4.0 (2 H, d, N·CH_2), and 1.23 (3 H, t, CH_2CH_3); $\lambda_{max.}$ (EtOH) 272.5 nm (ε 15 700); *m/e* (CI) 383 (M + 1) (Found: C, 66.3; H, 5.7; N, 7.45. $C_{21}H_{22}N_2O_5$ requires C, 66.0; H, 5.8; N, 7.3%).

N-*Benzyloxycarbonyl*-(Z)-*dehydrophenylalanine Thiobenzyl Ester.* Toluene-α-thiol (0.124 g, 1 mmol) was added to a stirred solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.28 g, 1 mmol) in chloroform (5 ml). After 48 h, no reaction was detected by t.l.c. or n.m.r. spectroscopy. Triethylamine (0.14 ml, 1 mmol) was added, and the mixture was stirred for a further 48 h, after which time t.l.c. showed no oxazolone to remain. Evaporation gave an oily solid which was triturated with ether (10 ml). The triturate was evaporated to a small volume and light petroleum was added giving a chromatographically homogeneous solid (0.35 g, 87%). Recrystallisation from ether–light petroleum gave *thiol ester* as needles, m.p. 101—102°; $\nu_{max.}$ ($CHCl_3$) 1 725, 1 665, and 1 620 cm^{-1}; δ($CDCl_3$) 7.5—7.2 (16 H, m, ArH and PhCH:C), 5.1 (2 H, s, $PhCH_2O$), and 4.18 (2 H, s, $PhCH_2S$); $\lambda_{max.}$ 299 nm (ε 19 700); *m/e* (CI) 404 (M + 1) (Found: C, 71.4; H, 5.3; N, 3.5; S, 8.2. $C_{24}H_{21}NO_3S$ requires C, 71.4; H, 5.25; N, 3.5; S, 7.95%).

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Grignard Reagents.* A *Phenylmagnesium bromide.* A suspension of (−)-2-benzyloxy-4-benzylideneoxazol-5-one (0.6 g, 2.15 mmol) in ether (20 ml) was added over 0.5 h to a stirred solution of phenylmagnesium bromide, prepared from bromobenzene (1.2 g, 7.6 mmol), in ether (8 ml). The mixture was heated at reflux for 1.75 h and was acidified with saturated ammonium chloride. The organic layer was dried and evaporated to give an oil (1.03 g), which was triturated with light petroleum (150 ml). Evaporation gave an oil, which was washed with a further portion of light petroleum (5 ml) and dried. This material, which could not be crystallised, was shown by spectral and analytical methods to be (Z)-1,1-*diphenyl*-(2-*benzyloxycarbonylamino*)*cinnamyl alcohol* (0.43 g, 46%), R_F (ether) 0.55; δ($CDCl_3$) 7.1—7.4 (20 H, m, ArH), 6.45br (1 H, s, NH), 5.82 (1 H, s, PhCH:C), and 4.85 (2 H, s, $PhCH_2$); δ_C($CDCl_3$; Me_4Si) 154.4 (C:O), 144.0 (aryl C), 137.8—127.5 (aryl C + C:C·NH), 124.2 (PhC:C), 82.3 (Ph_2C), and 67.2 p.p.m. ($PhCH_2$); *m/e* (CI) 418 (M^+ − OH) (Found: C, 80.3; H, 6.0; N, 3.2. $C_{29}H_{25}NO_3$ requires C, 80.0; H, 5.8; N, 3.2%). The same alcohol was obtained when the reaction was performed in the presence of copper(I) chloride.

B *Methylmagnesium iodide.* (*Z*)-2-Benzyloxy-4-benzylideneoxazol-5-one (2.0 g, 7.2 mmol) was added in portions over 0.5 h to a stirred solution of methylmagnesium iodide, prepared from methyl iodide (1.5 g, 12 mmol), in ether (25 ml) at 0°. The mixture was stirred at room temperature for 1.5 h, and ice was added to the solution, which was then partitioned between ethyl acetate and M-hydrochloric acid. The organic phase was dried and evaporated to give an oil which was placed on a silica column and eluted with ether. The first major fraction, R_F 0.6, was shown to consist largely of unchanged oxazolone (*ca.* 0.3 g). The second major fraction, R_F 0.35, comprised a chromatographically homogeneous yellow oil (0.93 g), which crystallised from light petroleum to give (Z)-1,1-*dimethyl*-(2-*benzyloxycarbonylamino*)*cinnamyl alcohol* (0.93 g, 50%) as a pale cream solid, m.p. 70—71°; R_F (ether) 0.35; δ($CDCl_3$) 7.3 (10 H, m,

ArH), 6.45br (1 H, s, NH), 6.32 (1 H, s, PhC*H*:C), 5.0 (2 H, s, $PhCH_2O$), 3.3br (1 H, s, OH), and 1.45 (6 H, s, 2 × CH_3); δ_C($CDCl_3$; Me_4Si) 154.7 (C:O), 138.9 (N·*C*:C), 136.1—127.1 (aryl C), 119.7 (Ph*C*:C), 72.5 (Me*C*OH), 67.05 ($PhCH_2O$), and 28.1 p.p.m. (CH_3·C); $\lambda_{max.}$ (EtOH) 260 nm (ε 15 250); *m/e* (CI) 312 ($M^+ + 1$) (Found: C, 73.2; H, 6.7; N, 4.6. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%).

C *Ethylmagnesium bromide.* (*Z*)-2-Benzyloxy-4-benzylideneoxazol-5-one (2.79 g, 10 mmol) was treated with ethylmagnesium bromide according to the procedure under B above, and the product was isolated analogously, giving (Z)-1,1-*diethyl*-(2-*benzyloxycarbonylamino*)*cinnamyl alcohol* as a yellow oil (1.6 g, 57%); δ($CDCl_3$) 7.25 (11 H, m, ArH + NH), 6.27 (1 H, s, CH:C), 5.07 and 4.91 (2 H, 2s, $PhCH_2O$), 2.55br (1 H, s, OH), 1.66 (4 H, qt, 2 × Me*CH*$_2$), and 0.88 (6 H, t, 2 × CH_3); $\lambda_{max.}$ (EtOH) 257.5 nm (ε 11 000); *m/e* (EI) 339 ($M^{\cdot+}$) (Found: C, 74.2; H, 7.5; N, 3.85. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.4; N, 4.1%).

Reduction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Lithium Aluminium Hydride.* A solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.8 g, 2.9 mmol) in tetrahydrofuran (7 ml) and ether (20 ml) was added dropwise, over 0.5 h, to a stirred suspension of lithium aluminium hydride (2.4 g, 63 mmol) in ether (75 ml), keeping the temperature below −40°. The mixture was stirred for a further 3 h, keeping the temperature below −30°. Ethyl acetate (20 ml) was added, and the solution was acidified with saturated ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried and evaporated to give an oily solid (0.75 g). Trituration with ether (5 ml) gave a solid (0.43 g), and evaporation of the liquors gave an oil, which was shown by t.l.c. and n.m.r. spectroscopy to be mainly benzyl alcohol. The solid was recrystallised from chloroform–light petroleum to give (Z)-4-*benzylideneoxazolidine*-2-*one* (0.372, 73%) as needles, δ($CDCl_3$) 8.03br (1 H, s, NH), 7.4—7.15 (5 H, m, ArH), 5.45 (1 H, t, PhCH:C), and 5.05 (2 H, d, *J* 2.0 Hz, CH_2O); $\lambda_{max.}$ (EtOH) 268 nm (ε 24 600) (Found: C, 68.8; H, 5.25; N, 8.1. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%).

Benzyloxycarbonyl-(Z)-*dehydrophenylalanine Hydrazide.*—Hydrazine hydrate (0.44 ml, 8.8 mmol) was added to a stirred solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (0.825 g, 2.96 mmol) in tetrahydrofuran (7.5 ml) at 0°. A thick precipitate formed within 30 s and a further portion of THF (5 ml) was added to facilitate stirring. After 10 min, t.l.c. showed no oxazolone to remain. The precipitate was collected by filtration, washed with ether, dried (0.71 g, 77%), and recrystallised from tetrahydrofuran–light petroleum to give the *hydrazide* as needles, m.p. 180—180.5°, δ([$^2H_6$]DMSO) 9.4br (1 H, s, N–H), 7.6—7.2 (10 H, m, ArH), 6.97 (1 H, s, PhCH:C), 5.02 (2 H, s, $PhCH_2$), and 5.0—3.5 (3 H, NH_2 + ½H_2O) (Found: C, 64.0; H, 5.6; N, 13.25. $C_{17}H_{17}N_3O_3$,½H_2O requires C, 63.7; H, 5.7; N, 13.1%). When this reaction was performed with warming, substantial amounts of the triazine described below were formed.

Reaction of Benzyloxycarbonyl-(Z)-*dehydrophenylalanine Hydrazide with* M-*Sodium Hydroxide.* A suspension of *N*-benzyloxycarbonyldehydrophenylalanine hydrazide (0.2 g, 0.625 mmol) in sodium hydroxide (M; 10 ml) was stirred for 1.25 h at room temperature, after which time dissolution was complete and t.l.c. showed no hydrazide to remain. Acidification to pH 1 with 6M-hydrochloric acid precipitated a solid which was collected and dried, giving (Z)-5-*benzylidene*-as-*triazine*-3,6-*dione* (75 mg, 59%), m.p. 234—237°; δ([$^2H_6$]DMSO) 10.66br (1 H, s, C·NH·CO), 7.7—7.25 (5 H, m, ArH), 6.52 (1 H, s, PhCH:C), and variable shift (2 H, br, CO·NHNH·CO); *m/e* (EI) 203 ($M^{\cdot+}$) (Found: C, 58.9; H, 4.4; N, 20.5. $C_{10}H_9N_3O_2$ requires: C, 59.1; H, 4.5; N, 20.7%).

Benzyloxycarbonyl-(Z)-*dehydrophenylalanine Phenylhydrazide.*—(*Z*)-2-Benzyloxy-4-benzylideneoxazol-5-one (0.83 g, 3 mmol) in THF (8 ml) was added dropwise over 5 min to a stirred solution of phenylhydrazine (0.402 g, 3.7 mmol) in THF (10 ml) at 0°. After 1 h the solution was evaporated and the residual foam was triturated with light petroleum. The resulting pale yellow solid was washed with ether and dried, giving chromatographically homogeneous *benzyloxycarbonyl*-(Z)-*dehydrophenylalanine phenylhydrazide* (1.05 g, 90%). Recrystallisation from ethyl acetate–light petroleum gave the *hydrazide* as cream crystals, m.p. 181—183° δ([$^2H_6$]DMSO) 10.05br (1 H, s, NH), 8.97br (1 H, s, NH), 7.7—6.5 (16 H, m, ArH + NH + PhCH:C), and 5.08 (2 H, s, $PhCH_2$) (Found: C, 71.1; H, 5.3; N, 11.1. $C_{23}H_{21}N_3O_3$ requires C, 71.3; H, 5.5; N, 10.85%).

Reaction of Benzyloxycarbonyl-(Z)-*dehydrophenylalanine Phenylhydrazide with* M-*Sodium Hydroxide.* A suspension of *N*-benzyloxycarbonyl-(Z)-dehydrophenylalanine phenylhydrazide (194 mg, 0.5 mmol) was stirred in sodium hydroxide (M; 5 ml) for 30 h, after which time t.l.c. showed no hydrazide to remain. The resulting solution was acidified to pH 1 with 6M-hydrochloric acid, and the resulting precipitate was collected, washed with water, and dried. This material (55 mg) appeared by n.m.r. to be a mixture and t.l.c. (Merck silica gel plates eluted with 1 : 2 : 17 acetic acid–methanol–chloroform) showed two spots of about equal intensity (u.v.) at R_F 0.2 (ninhydrin positive) and 0.25 (no reaction with ninhydrin); δ([$^2H_6$]DMSO) 10.9br, 8.67br, 7.23br, and 7.96br (4 s, exchange with D_2O) and 7.8—6.4 (m, no exchange with D_2O). This mixture could not be resolved by differential solvent extraction, nor could sufficient separation be achieved on ordinary preparative layer chromatography plates. The mixture was separated on a very small scale on a Merck silica gel analytical t.l.c. plate eluted with 1 : 2 : 17 acetic acid–methanol–chloroform, sufficient material being obtained for mass spectral analysis. The higher R_F material showed *m/e* (EI) 279 ($M^{\cdot+}$), 236, 208, 167, 107, 91 of relative abundance 6, 3, 18, 9, 20, and 25% respectively. The lower R_F material showed *m/e* (EI) 279 ($M^{\cdot+}$), 264, 210, 189, 149, 117, 108, 105, 92, and 91 of relative abundance 7, 3, 6, 6, 6, 25, 20, 22, 23, and 46% respectively. The components were assigned the isomeric structures (Z)-5-*benzylidene*-2-*phenyl*-as-*triazine*-3,6-*dione* (of higher R_F) and (Z)-1-*anilino*-4-*benzylideneimidazolidine*-2,5-*dione* (of lower R_F) (Found: C, 68.4; H, 5.0; N, 14.7. $C_{16}H_{13}N_3O_2$ requires C, 68.8; H, 4.7; N, 15.0%).

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Hydroxylamine.*—Solutions of 8% methanolic hydroxylamine hydrochloride (12 ml, 13.8 mmol) and 12% methanolic potassium acetate (12 ml, 14.7 mmol) were combined and the resulting potassium chloride precipitate was removed by filtration. (*Z*)-2-Benzyloxy-4-benzylideneoxazol-5-one (1.0 g, 3.6 mmol) was added to the stirred filtrate. After 24 h, the mixture was evaporated and the resulting oil was partitioned between M-hydrochloric acid and ethyl acetate. The organic layer was then extracted with saturated sodium hydrogencarbonate, and dried. Evaporation and trituration with ether gave chromatographically homogeneous

benzyloxycarbonyl-(Z)-dehydrophenylalanine hydroxamic acid (0.42 g, 37%). Recrystallisation from chloroform–light petroleum gave *hydroxamic acid* as crystals, m.p. 122—123° (decomp.); δ([$^2H_6$]DMSO) 8.85br (1 H, s, OH), 7.7—7.25 (10 H, m, ArH), 6.93 (1 H, s, PhCH:C), and 5.05 (2 H, s, $PhCH_2$) (Found: C, 65.0; H, 5.4; N, 8.7. $C_{17}H_{16}N_2O_4$ requires C, 65.4; H, 5.2; N, 9.0%).

Acidification of the yellow sodium hydrogencarbonate extracts to pH 1 with 6M-hydrochloric acid gave an oil which was extracted into ethyl acetate. The organic phase was dried and evaporated to give a solid, which was washed with ether, giving (Z)-1-*hydroxy*-4-*benzylideneimidazolidine*-2,5-*dione* as a solid (130 mg, 18%), m.p. 215° (decomp. starts 180°); δ([$^2H_6$]DMSO) 10.7br (2 H, s, NH + OH), 7.7—7.3 (5 H, m, ArH), and 6.56 (1 H, s, PhCH:C); *m/e* (EI) 204 ($M^{+\cdot}$) (Found: C, 58.6; H, 4.2; N, 13.45. $C_{10}H_8N_2O_3$ requires C, 58.8; H, 3.95; N, 13.7%).

A solution of the hydroxamic acid in hexadeuteriodimethyl sulphoxide decomposed to the imidazolidinedione on standing (complete in 5 h at room temperature).

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Aniline.*—Aniline (0.36 g, 3.85 mmol) was added to a stirred solution of 2-benzyloxy-4-benzylideneoxazol-5-one (0.98 g, 3.5 mmol) in THF (10 ml). After 20 h t.l.c. showed no oxazolone to remain and the solution was evaporated. The residual oil was partitioned between M-hydrochloric acid and ethyl acetate. The organic layer was dried and evaporated to give chromatographically homogeneous *benzyloxycarbonyl-(Z)-dehydrophenylalanine anilide* (1.02 g, 78%). Recrystallisation from chloroform–light petroleum gave *anilide* as needles, m.p. 131—131.5°; δ($CDCl_3$) 8.76br (1 H, s, NH), 7.6—6.8 (17 H, m, ArH + NH + PhCH:C), and 4.94 (2 H, s, $PhCH_2$) (Found: C, 73.85; H, 5.4; N, 7.6. $C_{23}H_{20}N_2O_3$ requires C, 74.2; H, 5.4; N, 7.5%).

Reaction of Benzyloxycarbonyl-(Z)-dehydrophenylalanine Anilide with M-*Sodium Hydroxide.*—A suspension of *N*-benzyloxycarbonyldehydrophenylalanine anilide (300 mg, 0.8 mmol) in sodium hydroxide (M; 10 ml) was stirred for 2.5 h, after which time t.l.c. showed no anilide to remain. Acidification to pH 1 with 6M-hydrochloric acid precipitated a solid which was collected, washed with water and chloroform, and dried giving (Z)-1-*phenyl*-4-*benzylideneimidazolidine*-2,5-*dione* (178 mg, 84%), m.p. 200° (decomp.); δ([$^2H_6$]DMSO) 9.3br (1 H, s, NH) and 8.3—6.6 (11 H, m, ArH + PhCH:C); *m/e* (EI) 264 ($M^{+\cdot}$) (Found: C, 69.95; H, 4.9; N, 10.05. $C_{16}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$ requires C, 70.3; H, 4.8; N, 10.25%).

Reaction of Benzyloxycarbonyl-(Z)-dehydrophenylalanylglycine Ethyl Ester with 0.5M-*Sodium Hydroxide.*—A suspension of *N*-benzyloxycarbonyldehydrophenylalanylglycine ethyl ester (150 mg, 0.39 mmol) in sodium hydroxide (0.5M; 2 ml) was stirred for 8 h. The clear solution was acidified to pH 1 with 6M-hydrochloric acid and the resulting precipitate was collected, washed with ether and water, and dried, giving (Z)-4-*benzylideneimidazolidine*-2,5-*dione* (62 mg, 64%), m.p. 225—270° (decomp.); δ([$^2H_6$]DMSO) 10.9br (1 H, s, NH), 7.75—7.3 (5 H, m, ArH), 6.58 (1 H, s, PhCH:C), and 4.2 (2 H, s, N·CH_2) (Found: C, 58.1; H, 4.3; N, 11.0. $C_{12}H_{10}N_2O_4$ requires C, 58.5; H, 4.1; N, 11.4%). The compound was somewhat hygroscopic.

Reaction of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one with Diazomethane.* (*Z*)-2-Benzyloxy-4-benzylideneoxazol-5-one (0.75 g, 2.7 mmol) was added to a stirred solution of ethanol-free diazomethane, prepared from Diazald (5.8 g, 27 mmol) in ether (70 ml). After 16 h, i.r. showed no oxazolone to remain and dry nitrogen was bubbled through the solution to remove the excess of diazomethane. Evaporation gave a yellow oil (0.9 g), which was shown by t.l.c. to be a complex mixture with one major component. The oil was placed on a silica column and eluted with ether. The combined earlier fractions (150 mg) were a complex mixture, which was not resolved. The major fraction, R_F 0.55, was chromatographically homogeneous. Evaporation gave an oil, which solidified on trituration with light petroleum to give 2-*benzyloxy*-8-*phenyl*-1,10-*dioxa*-3,5,6-*triazadispiro*[4.4.0.2]*dodeca*-2,5-*diene* as a pale brown solid (300 mg, 32%). An analytical sample was recrystallised from ether–light petroleum to give the *dodecadiene* as pale brown needles, m.p. 105—106° (decomp.); R_F (ether) 0.55; $\nu_{max.}$ ($CHCl_3$) 1 660, 1 600, 1 380, 1 280, 960, and 890 cm^{-1}; δ($CDCl_3$) 7.2 (10 H, m, ArH), 4.93 (1 H, d, *J* 12 Hz, PhC*H*HO), 4.77 (2 H, m, AB portion of ABX system, J_{AB} 15 Hz, CH_2·N:N), 4.66 (1 H, d, *J* 12 Hz, PhCH*H*O), 4.52 (1 H, d, *J* 11.5 Hz, OC*H*HC), 3.98 (1 H, d, *J* 11.5 Hz, Ph,CH*H*O), 3.07 (1 H, d, *J* 4.1 Hz, CC*H*HO), 2.98 (1 H, m, X portion of ABX system, J_{AX} 7.9 Hz, PhCH), and 2.78 (1 H, d, *J* 4.1 Hz, CCH*H*O); δ_C($CDCl_3$; Me_4Si) 153.1 (O·C:N), 135.1 135.6 (aryl C), 129.6—127.1 (aryl C), 99.0 (N·C·N), 82.6 (CH_2·N:N), 70.2 (O·*C*H_2C), 69.3 ($PhCH_2O$), 54.3 (*C*OCH_2), 49.0 (cyclopropyl CH_2), and 43.7 p.p.m. (PhCH); *m/e* (EI) 349 ($M^{+\cdot}$) (Found: C, 68.6; H, 5.6; N, 11.9. $C_{20}H_{19}N_3O_3$ requires C, 68.75; H, 5.4; N, 12.0%). The same product was obtained when the reaction was performed under conditions which give [9] a 1 : 1 adduct in the case of the corresponding thiazol-5-one.

Photolysis of (Z)-2-*Benzyloxy*-4-*benzylideneoxazol*-5-*one.*—A solution of (*Z*)-2-benzyloxy-4-benzylideneoxazol-5-one (100 mg, 0.36 mmol) in degassed propan-2-ol (100 ml) was irradiated for 20 h with 350 nm radiation in a Rayonet apparatus, after which time u.v. showed no oxazolone to remain. Evaporation gave N-*benzyloxycarbonylbenzylcarboximidic acid isopropyl ester* (103 mg, 92%) as an oil; $\nu_{max.}$ ($CHCl_3$) 1 710 and 1 660 cm^{-1}; δ($CDCl_3$) 7.3 (5 H, s, ArH), 7.2 (5 H, s, ArH), 5.11 (2 H, s, $PhCH_2O$), 5.06 (1 H, septet, Me_2CH), 3.63 (2 H, s, $PhCH_2C$), and 1.18 [6 H, d, *J* 6.1 Hz, $(CH_3)_2C$]; δ_C($CDCl_3$; Me_4Si) 167.2 and 161.3 (C:O and C:N), 135.8 and 134.5 (aryl C), 129.1—126.9 (aryl C), 70.6 (Me_2CH), 68.1 ($PhCH_2O$), 39.1 ($PhCH_2C$), and 21.3 p.p.m. (CH_3); *m/e* (EI) 311 ($M^{+\cdot}$) (Found: C, 72.9; H, 6.6; N, 4.6. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%).

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