Mechanism of Reaction of 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) with Nucleophiles and its Crystal Structure

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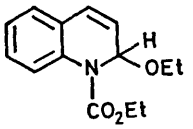
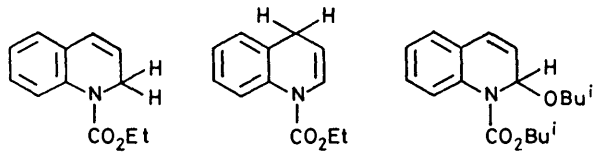
Hydrolysis of the title compound (1) occurs *via* reaction of the protonated species (16) with H_2O or HO^-. The high basicity of (1) [pK_a of ($1H^+$) is 4.22], which is necessary for high reactivity, is shown by analogues with 2-aryloxy- or 2-alkoxy-substituents, but not by 2-cyano-compounds [Reissert compounds (11)] or by 3,4-dihydroquinolines (10). 1-Aryl- or 1-alkyl-oxycarbonyl-substituents have the largest effect on reactivity [*e.g.* the pK_a of ($14H^+$) is 2.3 and its rate of reaction is increased 160-fold relative to ($1H^+$)] suggesting that reaction of nucleophile initially occurs at this site. Both acetate and amine (trifluoroethylamine) buffers react with (1) by similar mechanisms involving reaction between ($1H^+$) and either AcO^- or free amine; the reaction-rate–pH profiles are 'bell-shaped.' A new mechanism for the reaction of (1) as a reagent to promote peptide synthesis is suggested. Crystals of (1) are monoclinic, space group $P2_1/n$, with $Z = 4$ in a unit cell of dimensions $a = 12.608(2)$, $b = 7.644(1)$, $c = 13.374(2)$ Å, $\beta = 99.06(2)°$. The structure was determined by direct methods from four-circle diffractometer data and refined to a final R value of 5.47% from 1 490 observed reflections.

SINCE 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1) was first reported by Belleau *et al.*,[1] it has attracted considerable attention from among chemists, biochemists, and pharmacologists. It possesses both potent central-nervous-system depressant activity and is a selective irreversible inhibitor of the adrenergic α-receptor.[1] It was also found to promote the coupling in high yield of acylamino-acids and amino-acid esters.[1] In addition it has proved a valuable reagent in condensation reactions comparable to *NN*-dicyclohexylcarbodi-imide (DCC),[2-4] and is perhaps even superior to it.[5] It is interesting to speculate whether these diverse properties arise from a similar mechanism of action.



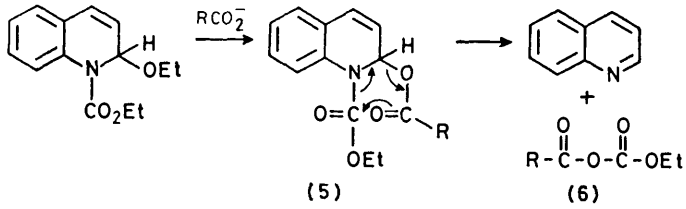
(1)

Some structures related to EEDQ also show similar properties. For example, low oral doses of 1-ethoxycarbonyl-1,2-dihydroquinoline (2) and 1-ethoxycarbonyl-1,4-dihydroquinoline (3) produced a progressive decrease in responsiveness and locomotor activity.[1] Similarly Kiso and Yajima[6] found 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (4) preferable to EEDQ as a coupling agent.



(2) (3) (4)

Belleau[1] suggested that EEDQ may be a selective activator of carbonyl functions, smoothly transforming them into mixed anhydrides (Scheme 1). Thus the carboxylate anion replaces the ethoxy-group in the 2-position giving the intermediate (5) which rapidly breaks down to give the mixed anhydride (6). The intermediate (5) was not isolated but evidence for the presence of the mixed anhydride was given (i.r., n.m.r., and mass spectrometry).[7] In coupling reactions between carboxylic acids and amines, the mixed anhydride (6) was suggested as the active acyl transfer agent. An additional postulate by Belleau[8] was that α-receptors may bear analogy to the carboxyserine hydrolyses, the carboxy-group being transformed into a mixed anhydride by EEDQ, thereby rendering the α-receptor inactive.



SCHEME 1

This mechanism requires the displacement of ^-OEt by the weak nucleophile RCO_2^- in the absence of a catalyst, which seems intuitively unlikely. We have therefore examined the structural effects which govern the reactivity of substituted 1,2-dihydroquinolines in order to determine the initial site of attack and propose a new mechanism of reaction.

RESULTS AND DISCUSSION

Hydrolysis of EEDQ.—The hydrolysis of EEDQ was examined for aqueous solutions at 25 °C (μ 1.0, KCl). Rate constants were determined from the change in optical density (o.d.) at 260 nm at pH values >4.2 and at 330 nm for those <4.2. The products formed under these conditions at all pH values were quinoline, ethanol, and carbon dioxide. In general the rates of hydrolysis showed catalysis due to buffer species and the observed rate constants listed in Table 1 were determined spectrophotometrically, in the absence of buffers, using a pH-stat to maintain constant pH.[9] Where buffers were

used, extrapolation to zero buffer concentration gave the same buffer–independent water rate as obtained in the absence of buffers.

The plot of log k_{obs} *vs.* pH (Figure 1) clearly shows that the hydrolysis of EEDQ is acid-catalysed at high pH but becomes pH-independent at low pH. This behaviour is typical of a specific acid-catalysed process;

TABLE 1

Observed rate constants for the hydrolysis of EEDQ (1) at 25 °C in water

pH	$10^3 k_{obs}/s^{-1}$
0.12	4.12
1.0	7.17
2.0	7.66
2.5	7.75
3.0	7.10
3.8	5.15
4.25	4.02
4.61	2.52
5.0	1.20
5.28	0.77
5.5	0.44
6.2	0.10

the curve in Figure 1 is theoretical, being drawn by use of equation (1) with k_1 7.94×10^{-3} s^{-1} and K $10^{-4.22}$.

$$k_{obs} = (k_1 a_H)/(K + a_H) \quad (1)$$

In addition, the unchanged EEDQ showed a pronounced spectral change on acidification (see Figure 2); the o.d. at 373 nm was recorded as a function of pH to give the titration curve of Figure 3. Because of the reactivity of EEDQ in acidic solution, the o.d. at this wavelength decreased with time; the values used to construct Figure 3 were therefore obtained by extra-

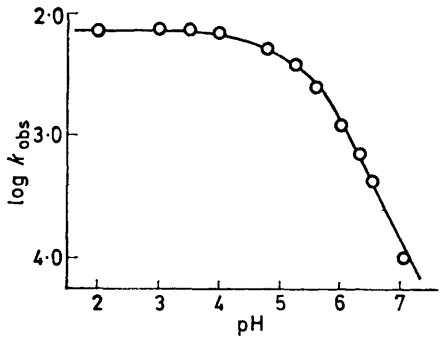


FIGURE 1 Plot of log k_{obs} (k_{obs} in s^{-1}) against pH for the hydrolysis of EEDQ (1) in water at 25 °C; the line is theoretical [from equation (1) with k_1 7.94×10^{-3} s^{-1} and K $10^{-4.22}$] and the points experimental

polation back to 0% reacted. These data give an apparent pK_a of 4.22 for EEDQ.

Clearly then, the unchanged substrate is undergoing a reversible pH-determined change (protonation–deprotonation) and the protonated form is the only reactive species at all pH values.

A significant solvent-isotope effect was also observed. Thus at pH 1.55 (25 °C), k_{obs} 2.52×10^{-3} s^{-1} in D_2O. This threefold decrease in rate in D_2O is consistent with rate-determining attack by water on the protonated substrate. The isotope effect was measured on the pH-independent plateau at low pH to minimise any uncertainty due to changes in the substrate pK on changing the solvent.

A simple mechanism to account for these observations is summarised in Scheme 2. This involves rate-determining water attack on protonated (1); the tetrahedral

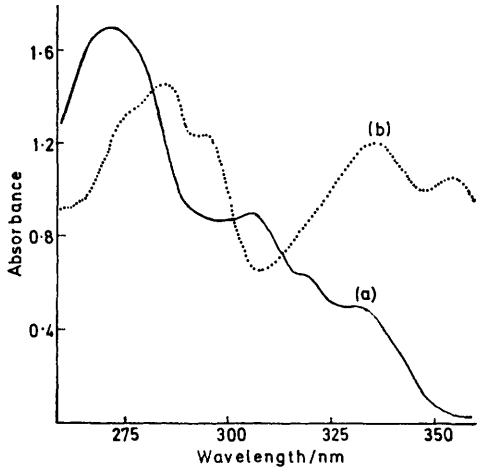


FIGURE 2 U.v. spectra of (13) [similar to that of EEDQ(1)] (a) in neutral solution, (b) at pH 1.0

intermediate formed can then break down either directly (*via* path *b*) to give quinoline or (*via* path *a*) to the carbamate (9), which in turn undergoes concerted loss of CO_2 and ethoxide ion. Two major problems however remain: determination of the site of attack of other nucleophiles, and the site of protonation of EEDQ. The latter problem arises since simple carbamates such as ethyl *NN*-dimethylcarbamate have pK_a close to zero.[10-12] If the protonation site is therefore the carbamate side-chain of (1) (and there are no other apparent

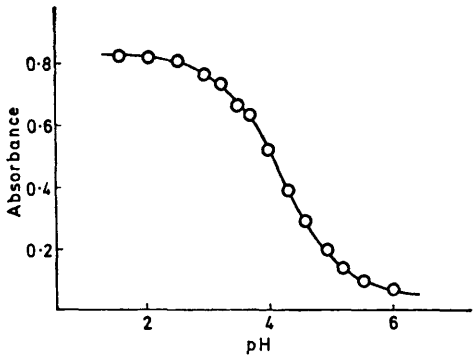
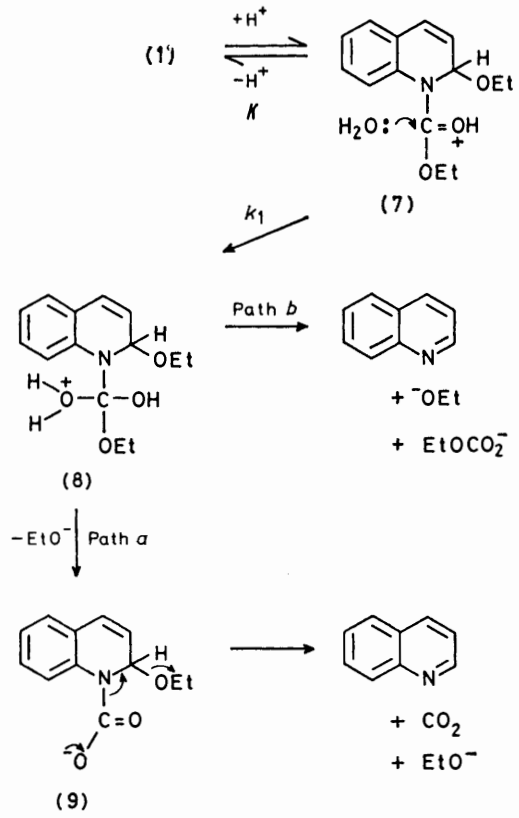


FIGURE 3 Plot of optical density of EEDQ (1) in water at 25 °C against pH; the line is theoretical assuming a pK_a of 4.22

basic groups), then other structural features peculiar to EEDQ must be responsible for raising the basicity of (1) by some four powers of ten. We have therefore examined a number of structural analogues of EEDQ to discover which groups are necessary for its high hydrolytic reactivity.

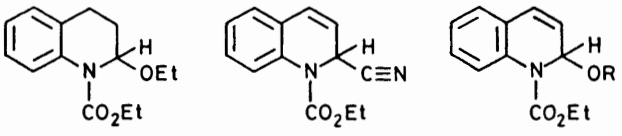
EEDQ *Analogues*.—(i) 2-Ethoxy-1-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline (10) was unreactive in water

over the pH range 0—14 at 25 °C. Neither does (10) show the characteristic spectral change shown by (1) about pH 4, the same absorbance ($\lambda_{max.}$ at 273 nm) being observed from pH 0—14. In concentrated hydrochloric acid however a yellow solution of (10) is formed and the substrate has a $\lambda_{max.}$ 328 nm. Similar



SCHEME 2

behaviour was noted in concentrated sulphuric acid; in both cases the substrate underwent slow hydrolysis in concentrated acid. Clearly the presence of the double bond at the 3,4-position is necessary both for the high reactivity and enhanced basicity shown by EEDQ. The reactivity pattern shown by (10) is similar to that



observed with other simple *NN*-disubstituted carbamates.[11,12]

(ii) 2-Cyano-1-ethoxycarbonyl-1,2-dihydroquinoline (11) was also found to be unreactive over the entire pH region; in addition its u.v. spectrum was identical ($\lambda_{max.}$ 267 nm) from pH 0—14. It is thus likely that the presence of oxygen at the 2-position is essential in assisting protonation of EEDQ.

(iii) The rates of hydrolysis of a series of 2-alkoxy- and 2-aryloxy-derivatives (12; R = Me, Et, CF_3CH_2, or Ph) were measured in the pH range 1.0—2.5. The rates of hydrolysis were in each case independent of pH [as previously observed for (1)], but interestingly were all similar in magnitude (see Table 2). This would appear

TABLE 2

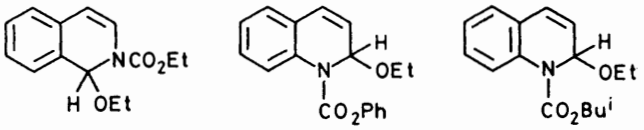
Average rate constants for the hydrolysis of 1,2-dihydroquinolines (12) in pH region 1.0—2.5 in water at 25 °C

Substrate, R =	$10^3 k_{obs}/s^{-1}$
Me	7.3
Et	7.6
CH_2CF_3	6.2
Ph	7.0

to rule out a mechanism involving rate-determining loss of the 2-alkoxy-group (as originally suggested by Belleau *et al.*[1]), since the groups studied vary widely in leaving-group ability.

Each of the substrates (12) had an apparent pK in the same region as did (1) and showed a similar shift to longer wavelength (see Figure 2) on protonation. This lends support to the hypothesis that the presence of the 2-alkoxy-group is essential for protonation of EEDQ analogues.

(iv) The isoquinoline analogue of EEDQ, 1-ethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinoline (13) in general showed a similar reactivity to EEDQ itself. Thus hydrolysis at low pH was pH-independent (k_{obs} 4.0 × 10^{-3} s^{-1} in pH region 1.0—2.0) the products being isoquinoline, ethanol, and carbon dioxide. The dihydro-



isoquinoline (13) also shows similar spectral behaviour to EEDQ and had an apparent pK_a in the same region.

(v) *Variation of the* 1-*alkoxycarbonyl substituent.* A major change in reactivity was observed when the 1-ethoxycarbonyl substituent of (1) was changed to a 1-phenoxycarbonyl (14) (See Table 3). Compound (14)

TABLE 3

Observed rate constants (s^{-1}) for the hydrolysis of 1-alkoxycarbonyl-2-alkoxy-1,2-dihydroquinolines in 2 : 3 dioxan–water at 25 °C

Substrate	pH	$10^3 k_{obs}/s^{-1}$
(4)	1.0	2.42
	1.7	2.48
	2.3	2.18
(15)	1.0	2.33
	1.7	2.44
	2.3	2.18
(1)	1.0	1.78
	1.7	1.75

showed a pH–rate profile broadly similar to that of (1) (Figure 1) except that the apparent pK_a was shifted approximately 2 units (to 2.3) and the reactivity of the

protonated form was enhanced *ca.* 160-fold [equation (1) was followed with $k_1 = 1.26$ s^{-1} and $K = 10^{-2.3}$]. At high pH ($a_H \ll K$), both (1) and (14) react at much the same rate, because of cancelling of changes in k_1 and K values [see equation (1)].

The reduced basicity of (14) relative to (1) is consistent only with protonation adjacent to the phenyl group, *i.e.* on either of the carbamate oxygens. Moreover, the increased reactivity of protonated (14) relative to protonated (1) is good evidence that breakdown of the tetrahedral intermediate (8) is kinetically important and most likely occurs *via* loss of the alkoxy- (or phenoxy-) group (path *a*, Scheme 2).

(vi) *Bulky groups.* We also examined the effect of branched alkyl groups in the 1- and 2-positions on the reactivity of 1,2-dihydroisoquinolines. The substrates used were the di-isobutyl-derivative (4) and 2-ethoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (15). Because (4) and (15) were insufficiently soluble in water, the rates of hydrolysis of the protonated substrates were examined in 2 : 3 (v/v) dioxan–water at 25 °C; for comparison, hydrolytic data for EEDQ measured under the same conditions is also presented (Table 3). It is clear that all three substrates react at quite similar rates (the marginally faster rate of reaction of (4) probably accounts for its reported superiority, relative to EEDQ for promoting condensations). Thus bulky groups do not inhibit protonation (and thus high reactivity) of these substrates.

Acetate Ion as Nucleophile.—It has been reported [6] that carboxylic acids react preferentially (relative to other nucleophiles) with EEDQ. A special mechanism (Scheme 1) was proposed to account for this and EEDQ was termed a 'special recognition site' for carboxylic acid anions. We have examined in some detail the reactivity of (1) in the acetic acid–acetate buffer system; the results are presented in Tables 4 and 5.

At pH values 4.8 and 5.6 the rate of reaction of EEDQ is directly proportional to the concentration of added buffer; extrapolated values of k_{obs} to zero buffer concentration were identical to those obtained by use of the pH-stat method in the absence of buffers.

TABLE 4

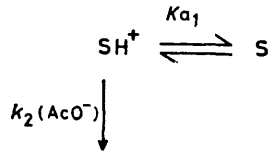
Observed rate constants (s^{-1}) for the reaction of EEDQ (1) at 25 °C with acetate buffers

[HOAc + $^-$OAc]/M	0.1	0.05	0.025	0.01
10^3k_{obs} (at pH 4.8)	21.0	11.2	6.3	3.5
10^3k_{obs} (at pH 5.6)	8.0	4.3	2.17	1.10

In order to determine the reactive species, the rate of reaction of EEDQ was examined over a wide pH range using a constant concentration (0.10M) of buffer (HOAc + $^-$OAc). The results obtained (Table 5) have been corrected for the background reaction with water (which is particularly important at low pH). The second-order rate constants, k_{B_T}, for reaction of EEDQ with 1.0M total acetate are plotted against pH in Figure 4. Clearly the reaction of EEDQ reaches a maximum at pH *ca.* 4.5 and decreases in acid and base. This bell-shaped curve was closely fitted by equation (2) with the following values for the constants: $K_{a1} = 10^{-4.22}$, $K_{a2} = 10^{-4.77}$, $k_2 = 0.36$ l mol^{-1} s^{-1} (Figure 4, solid line). Equation (2)

$$k_{B_T} = \frac{k_2 a_H K_{a1}}{a_{H^2} + a_H(K_{a1} + K_{a2}) + K_{a1}K_{a2}} \qquad (2)$$

was derived from the empirical reaction shown in Scheme 3, where S and SH^+ are the substrate (EEDQ) and



SCHEME 3

protonated substrate respectively and reaction is assumed to occur only between SH^+ and acetate ion (K_{a2} is the acidity constant for acetic acid). Since pK_{a1} and pK_{a2} are less than 2 units apart, equation (2) was solved by the method of Alberty and Massey.[13]

TABLE 5

Rate constants ($k_{obs} - k_0$) for the reaction of EEDQ (1) with 0.1M acetate buffers at 25 °C

pH	3.0	3.18	3.5	3.75	4.0	4.28
10^3k/s^{-1}	4.4	4.9	8.7	14.5	18.5	21.3
pH	4.5	4.6	5.0	5.3	5.5	6.0
10^3k/s^{-1}	23.0	21.0	18.3	13.0	8.9	2.24

It therefore appears that the reaction of EEDQ with acetic acid buffers is analogous to that with water, reaction occurring only *via* the protonated substrate. The observed rate decrease in acid solution (Figure 3) is due to decreasing {AcO$^-$} as SH^+ remains constant,

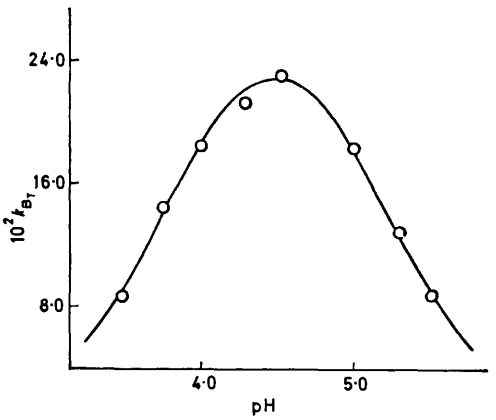


FIGURE 4 Plot of the observed rate of reaction of EEDQ (1) with 0.1M acetate buffer as a function of pH. The observed rate constants have been corrected for reaction of (1) with water; the line is theoretical (see text)

while the rate of reaction with acetate decreases at high pH because the concentration of SH^+ decreases with a_H in this region.

Trifluoroethylamine as Nucleophile.—One of the reasons that a special mechanism was suggested for the

reaction of (1) with AcO^- was the observation that other nucleophiles such as amines do not appear to react with (1).[14] However, this may be due to the fact that in the pH region where (1) is substantially protonated (and therefore reactive), the concentration of free amine present (pK_a typically *ca.* 10) is very low indeed. We have therefore examined the reactivity of (1) with trifluorethylamine, which is a typical primary amine, but with a pK_a of 5.8.[15]

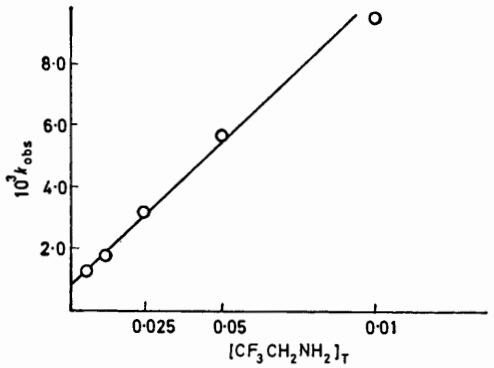
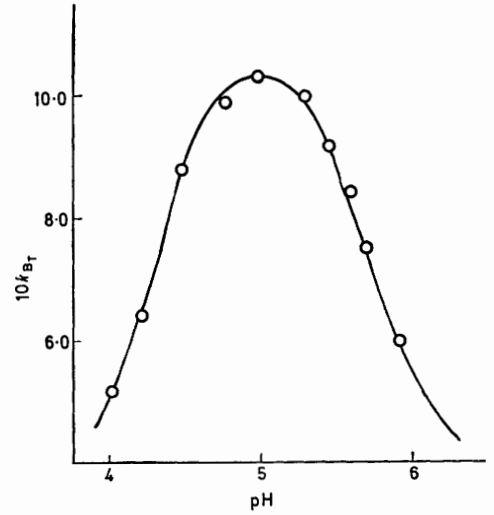


FIGURE 5 Observed rates of reaction of EEDQ (1) at pH 5.8 as a function of trifluoroethylaniline concentration (molar)

The results obtained (see Figure 5, a plot of observed rate against added trifluoroethylamine concentration) clearly show that the reaction of EEDQ is catalysed by this amine. When catalysis is measured as a function of pH (Figure 6), a bell-shaped curve is obtained; the theoretical line was drawn by use of equation (2) with K_{a1} $10^{-4.22}$, K_{a2} $10^{-5.8}$, and k_2 0.137 l mol^{-1} s^{-1}. Thus, by analogy with the empirical Scheme 3, reaction is also occurring between protonated EEDQ and free trifluoroethylamine in this case. Moreover the observed similar rates of raction of AcO^- and $CF_3CH_2NH_2$ with ($1H^+$)



IGURE 6 Observed rates of reaction of (1) with trifluoroethylamine buffer ($CF_3{\cdot}CH_2{\cdot}NH_2 + CF_3{\cdot}CH_2{\cdot}\overset{+}{N}H_3 = 0.10$M) as a function of pH. The observed rate constants have been corrected for reaction of (1) with water; the line is theoretical, drawn by use of equation (2) and the values of the constants given in the text

argues against a special mechanism for the AcO^- reaction; it has previously been shown [16] that the reactivities of these nucleophiles towards reactive esters are similar.

Crystal Structure of EEDQ.—Since EEDQ shows a remarkably high basicity for a substrate containing a carbamate moiety, we have examined its molecular structure by *X*-ray methods to discover whether any distortion or other unusual structural features are present. The crystal structure was determined by direct methods from four-circle diffractometer data, and refined by least-squares and difference-Fourier methods to a final *R* value of 5.47% for the 1 490 observed reflections. The molecular structure and atom-numbering system are shown in Figure 7, and the bond lengths, bond angles, and torsion angles are displayed in Table 6.

Although the N–C bond length of the amide bond (1.38 Å) is longer than that for simple amides (1.32 Å) or for the related ethyl *N*-phenylcarbamate (1.35 Å),[17] this is not accompanied by any appreciable distortion of the torsional angle of the amide group. Thus the atoms C(10), N(1), C(11), O(12), and O(13) are essentially coplanar (see Table 6). This would appear to rule out any enhanced basicity of the carbamate group [caused, for example, by interaction between the *peri*-hydrogen attached to C(9) and O(13)].

The carboxy-group is oriented towards C(2) [*i.e.* C(2)–N(1)–C(11)–C(12) is −11°]; this configuration has

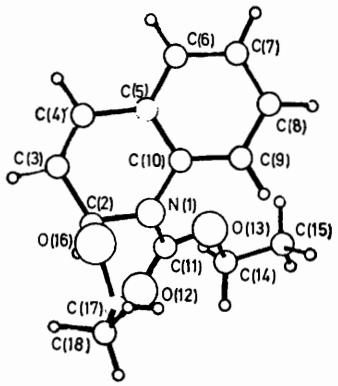


FIGURE 7 Structure and crystallographic atom numbering scheme for EEDQ (1)

been predicted from spectral measurements for Reissert compounds.[18]

The hydrogen attached to C(2) is in a pseudo-equatorial position while the more bulky ethoxy-group is in a pseudo-axial position. Deviations of H(2) and O(16) from the N(1), C(2), C(11) plane are −0.02 and 1.21 Å (see also torsion angles in Table 6). This conformation (with the more bulky group in a pseudo-axial position) is also consistent with n.m.r. measurements [19–22] on Reissert compounds.

It is difficult to envisage how this structure would show the enhanced basicity observed. However, the conformational change of ring inversion would bring O(16) into the plane of the O(12), C(11), N(1), and C(2) groups and thus be correctly oriented to assist in proton-

TABLE 6

Molecular geometry of EEDQ (1)

(*a*) Bond lengths (Å)

N(1)–C(2)	1.465(4)	C(7)–C(8)	1.380(6)
N(1)–C(10)	1.431(4)	C(8)–C(9)	1.386(4)
N(1)–C(11)	1.375(4)	C(9)–C(10)	1.384(4)
C(2)–C(3)	1.487(5)	C(11)–O(12)	1.205(3)
C(2)–O(16)	1.417(4)	C(11)–O(13)	1.329(4)
C(3)–C(4)	1.319(5)	O(13)–C(14)	1.461(4)
C(4)–C(5)	1.454(5)	C(14)–C(15)	1.474(6)
C(5)–C(6)	1.402(5)	O(16)–C(17)	1.430(5)
C(5)–C(10)	1.393(4)	C(17)–C(18)	1.507(6)
C(6)–C(7)	1.369(6)		

(*b*) Bond angles (°)

C(2)–N(1)–C(10)	117.4(2)	C(7)–C(8)–C(9)	120.5(3)
C(2)–N(1)–C(11)	116.2(2)	C(8)–C(9)–C(10)	119.9(3)
C(10)–N(1)–C(11)	125.5(2)	N(1)–C(10)–C(5)	117.3(3)
N(1)–C(2)–C(3)	110.6(2)	N(1)–C(10)–C(9)	122.6(3)
N(1)–C(2)–O(16)	111.6(2)	C(5)–C(10)–C(9)	120.1(3)
C(3)–C(2)–O(16)	108.0(2)	N(1)–C(11)–O(12)	124.7(3)
C(2)–C(3)–C(4)	121.0(3)	N(1)–C(11)–O(13)	111.6(2)
C(3)–C(4)–C(5)	121.0(3)	O(12)–C(11)–O(13)	123.7(3)
C(4)–C(5)–C(6)	122.2(3)	C(11)–O(13)–C(14)	115.6(2)
C(4)–C(5)–C(10)	118.9(3)	O(13)–C(14)–C(15)	106.9(3)
C(6)–C(5)–C(10)	118.9(3)	C(2)–O(16)–C(17)	113.5(3)
C(5)–C(6)–C(7)	120.8(3)	O(16)–C(17)–C(18)	108.3(4)
C(6)–C(7)–C(8)	119.9(3)		

(*c*) Torsion angles (°)

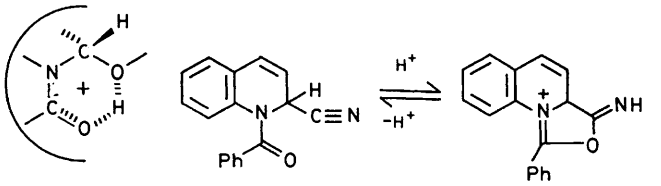
C(10)–N(1)–C(2)–C(3)	43.1
C(11)–N(1)–C(2)–C(3)	−126.3
C(2)–N(1)–C(10)–C(5)	−32.0
C(11)–N(1)–C(10)–C(9)	−44.4
C(10)–N(1)–C(11)–O(12)	−179.4
N(1)–C(2)–C(3)–H(3)	156.8
H(2)–C(2)–C(3)–C(4)	−146.6
C(3)–C(2)–O(16)–C(17)	166.3
C(2)–C(3)–C(4)–H(4)	177.9
C(3)–C(4)–C(5)–C(6)	−163.7
H(4)–C(4)–C(5)–C(10)	−164.2
C(10)–C(5)–C(6)–C(7)	−1.3
C(4)–C(5)–C(10)–C(9)	−177.3
C(5)–C(6)–C(7)–C(8)	0.5
H(6)–C(6)–C(7)–H(7)	0.3
H(7)–C(7)–C(8)–C(9)	−178.7
C(7)–C(8)–C(9)–H(9)	−180.0
C(8)–C(9)–C(10)–N(1)	179.8
H(9)–C(9)–C(10)–C(5)	179.2
C(11)–O(13)–C(14)–C(15)	−165.0
O(13)–C(14)–C(15)–H(15A)	−173.5
H(14A)–C(14)–C(15)–H(15A)	−64.8
H(14B)–C(14)–C(15)–H(15A)	67.9
C(2)–O(16)–C(17)–C(18)	−16.72
O(16)–C(17)–C(18)–H(18A)	−62.1
H(17A)–C(17)–C(18)–H(18A)	173.0
H(17B)–C(17)–C(18)–H(18A)	59.3
C(10)–N(1)–C(2)–O(16)	−77.2
C(11)–N(1)–C(2)–O(16)	113.4
C(2)–N(1)–C(10)–C(9)	147.3
C(2)–N(1)–C(11)–O(12)	−10.9
C(10)–N(1)–C(11)–O(13)	−0.3
O(16)–C(2)–C(3)–C(4)	95.8
H(2)–C(2)–C(3)–H(3)	36.8
H(2)–C(2)–O(16)–C(17)	43.1
H(3)–C(3)–C(4)–C(5)	174.5
C(3)–C(4)–C(5)–C(10)	15.0
C(4)–C(5)–C(6)–C(7)	177.4
C(10)–C(5)–C(6)–H(6)	177.3
C(6)–C(5)–C(10)–N(1)	−179.2
C(5)–C(6)–C(7)–H(7)	179.4
C(6)–C(7)–C(8)–C(9)	0.1
H(7)–C(7)–C(8)–H(8)	1.7
H(8)–C(8)–C(9)–C(10)	179.7
C(8)–C(9)–C(10)–C(5)	−0.9
N(1)–C(11)–O(13)–C(14)	−179.7
C(11)–O(13)–C(14)–H(14A)	84.1
O(13)–C(14)–C(15)–H(15B)	−53.4
H(14A)–C(14)–C(15)–H(15B)	55.3
H(14B)–C(14)–C(15)–H(15B)	−172.0

TABLE 6 (*Continued*)

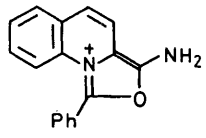
(*c*) Torsion angles (°)

C(2)–O(16)–C(17)–H(17A)	−40.0
O(16)–C(17)–C(18)–H(18B)	179.3
H(17A)–C(17)–C(18)–H(18B)	54.3
H(17B)–C(17)–C(18)–H(18B)	−59.3
C(10)–N(1)–C(2)–H(2)	168.0
C(11)–N(1)–C(2)–H(2)	−1.4
C(11)–N(1)–C(10)–C(5)	136.3
C(2)–N(1)–C(11)–O(13)	168.2
N(1)–C(2)–C(3)–C(4)	−26.6
O(16)–C(2)–C(3)–H(3)	−80.8
N(1)–C(2)–O(16)–C(17)	−71.9
C(2)–C(3)–C(4)–C(5)	−1.3
H(3)–C(3)–C(4)–H(4)	−6.3
H(4)–C(4)–C(5)–C(6)	17.1
C(4)–C(5)–C(6)–H(6)	−4.0
C(4)–C(5)–C(10)–N(1)	2.1
C(6)–C(5)–C(10)–C(9)	1.5
H(6)–C(6)–C(7)–C(8)	−178.0
C(6)–C(7)–C(8)–H(8)	−179.5
C(7)–C(8)–C(9)–C(10)	0.1
H(8)–C(8)–C(9)–H(9)	−0.4
H(9)–C(9)–C(10)–N(1)	−0.1
O(12)–C(11)–O(13)–C(14)	−0.6
C(11)–O(13)–C(14)–H(14B)	−44.5
O(13)–C(14)–C(15)–H(15C)	65.4
H(14A)–C(14)–C(15)–H(15C)	−174.2
H(14B)–C(14)–C(15)–H(15C)	−53.1
C(2)–O(16)–C(17)–H(17B)	69.5
O(16)–C(17)–C(18)–H(18C)	55.0
H(17A)–C(17)–C(18)–H(18C)	−70.0
H(17B)–C(17)–C(18)–H(18C)	176.4

ation of adjacent O(12) (16). Although a similar conformation is possible with isoquinolines (13) (which show EEDQ-like reactivity), saturation of the C(2)–C(4) linkage [as in (10)] destroys the close spatial relationship of the carbonyl and ethoxy-group oxygens.



(16) (17) (18)



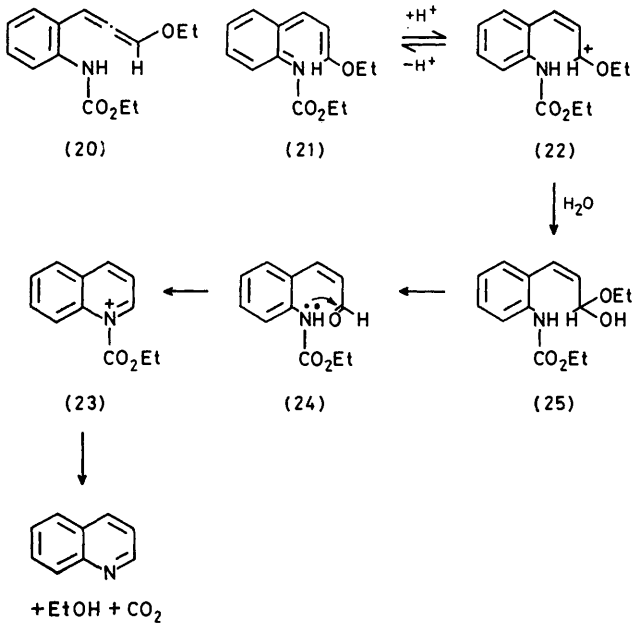
(19)

Reissert compounds are reactive only in strongly acid solution [23] and acid-catalysed formation of the cyclic cation (18) [or (19)] [24] has been suggested as the first step on the reaction pathway. However it is not possible to form cyclic structures analogous to (18) or (19) from (1) in acid solution.

The protonated structure (16) is also consistent with the observed variation in pK_a with the nature of the alkyl- or aryl-oxycarbonyl group, and with the variation in reactivity as the ethoxycarbonyl group is changed

(which is similar to that observed with acid-catalysed hydrolysis of simple carbamates).[11] The latter would also indicate that breakdown of the intermediate (8) occurs *via* path *a* (EtO^- as leaving group) rather than *via* path *b* (Scheme 2); if the alternative breakdown *via* path *b* were to occur one would expect little variation in rate when the ethoxycarbonyl group is changed but some sensitivity to the nature of the 2-alkoxy-group.

An alternative explanation for the high reactivity of (1) in acid solution might be sought in terms of ring opening–recyclization; however, it is more difficult to explain the observed substituent effects in these terms. It has been shown that species such as (20) [25] or (21) [26] are formed on irradiation of EEDQ at low temperature. Ring closure (to reform EEDQ) is complete at room temperature; the total reversibility is >99%. Structure (20) has no obvious basic site; however the nitrogen in (21) on protonation gives a stabilized allylic cation (22) and this might be sufficient to push the equilibrium between (1) and (21) to the open-chain form at low pH. Reaction of (22) with water gives a hemiacetal (25) which on rapid loss of EtOH [to give (26)] could recyclize *via* a carbamate nitrogen participation to give the observed products (Scheme 4). It is however difficult to



SCHEME 4

rationalize the observed substituent effects (on pK_a and reaction of protonated EEDQ) in terms of this Scheme.

Reaction of EEDQ *in Neutral and Basic Solution.*—Hydrolysis of (1) is slow at 25 °C at high pH. At elevated temperature however hydrolysis to quinoline, ethanol, and carbon dioxide was noted; the rate of hydrolysis is pH-independent from pH 7 to 13. At pH 14 there is a small increase in the rate of hydrolysis (Table 7) from which a second-order rate constant of 2×10^{-4} l mol^{-1} s^{-1} can be estimated for the reaction of (1) with HO^- at 55 °C. This most likely represents direct HO^- attack on (1) at the carbamate linkage since the carbamate Ph(Me)N·C(:O)·OEt (26) reacts with HO^- at a similar rate (2.0×10^{-5} l mol^{-1} s^{-1} at 25 °C).

The pH-independent rate (Table 6) therefore does not represent the attack of water (a much weaker nucleophile than HO^-) on (1) but rather the kinetically equivalent

TABLE 7

Observed rate constants for the hydrolysis of (1) at 55 °C (μ 1.0, KCl)

pH	7.6	10.65	12.5	14.0
$10^4 k_{obs}$/s^{-1}	7.20	6.96	7.53	9.25

HO^- reaction with the protonated species (16). On this basis a value of 2×10^3 l mol^{-1} s^{-1} is calculated for the reaction of (16) with HO^-, which is reasonable when compared with the value above for the reaction of (16) with H_2O.

In conclusion, the behaviour of EEDQ towards nucleophiles parallels that of other *NN*-disubstituted carbamates. EEDQ is 10^4-fold more reactive than expected, largely because it is protonated in the pH range 0—4, where other carbamates are present largely as the free base form. A possible explanation for the high basicity of EEDQ is the formation of a stabilized cyclic system (16). Reaction of EEDQ occurs preferentially with RCO_2^- rather than with strong amine bases at pH values close to the pK_a of EEDQ, since the concentration of free amine is very low in this region. The reactivity of EEDQ analogous can be greatly enhanced by variation of the *N*-alkoxycarbonyl group.

EXPERIMENTAL

General.—All inorganic materials used were AnalaR grade. Dioxan (B.D.H. AnalaR) was used without further purification. Deionized water was twice distilled from alkaline potassium permanganate. Most kinetic experiments were carried out in water; otherwise 3 : 2 (v/v) water–dioxan was used. The ionic strength was maintained at 1.0 by the addition of potassium chloride. The pH of solutions was maintained constant in the absence of buffers by the use of the combined pH-stat–u.v.-spectrophotometer which has been described previously.[27]

M.p.s were measured with an Electrothermal apparatus I.r. spectra were measured by use of a Perkin-Elmer PE 257 spectrophotometer, the solids being examined as KBr discs. N.m.r. spectra were run on a Perkin-Elmer 20A spectrometer.

Substrates.— 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (1) was prepared according to the method of ref. 28. On recrystallisation from light petroleum (b.p. 60—80 °C) it had m.p. 62—64 °C (lit.,[28] 63.5—65 °C); $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ(CD_3CN) 1.14 (m, 6 H), 3.57 (q, 2 H), 4.22 (q, 2 H), 6.12 (m, 2 H), 6.68 (m, 1 H), and 7.0—7.7 (m, 4 H) (Found: C, 67.95; H, 7.0; N, 5.85. Calc. for $C_{14}H_{17}NO_3$: C, 68.3; H, 6.9; N, 5.7%).

2-Isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (4) was prepared according to the method of ref. 6. The product was an oily liquid, b.p. 143—144 °C (0.1 mm), [lit.,[6] 144—145 °C (0.5 mm)]; $\nu_{max.}$ 1 705 cm^{-1} (C=O); δ(CH_3CN) 0.81 (m, 12 H), 1.79 (m, 2 H), 3.25 (d, 2 H),

3.92 (d, 2 H), 5.95 (q, 2 H), 6.46 (m, 1 H), and 6.93—7.60 (m, 4 H).

Similarly prepared was 2-ethoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (15), b.p. 140—141 °C (0.2 mm) [lit.,[6] 143—144 °C (0.2 mm)]; $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ(CD_3CN) 0.96 (q, 9 H), 1.92 (m, 1 H), 3.55 (q, 2 H), 3.95 (d, 2 H), 6.08 (quin, 2 H) 6.62 (m, 1 H), and 6.97—7.71 (m, 4 H).

2-Cyano-1-ethoxycarbonyl-1,2-dihydroquinoline (11) was prepared by the general procedure of ref. 29. Ethyl chloroformate (6.95 g, 0.064 mol) was added dropwise to a stirred mixture of quinoline (4.13 g, 0.032 mol) in methylene chloride (40 ml) and potassium cyanide (6.25 g, 0.096 mol) in water (15 ml). When addition was complete the mixture was stirred for 3 h. The layers were separated and the organic layer was washed with water, 10% hydrochloric acid, 10% sodium hydroxide, and again with water. Evaporation of the methylene chloride yielded an oil [$\nu_{max.}$ 2 245 cm^{-1} (w, CN)] which was dissolved in chloroform and reprecipitated as a yellow-brown solid with light petroleum (b.p. 60—80 °C). The dihydroquinoline had m.p. 61—63 °C (Found: C, 68.2; H, 5.55; N, 12.1. $C_{13}H_{12}N_2O_2$ requires C, 68.5; H, 5.3; N, 12.3%), $\nu_{max.}$ 1 720 cm^{-1} (C=O); δ($CHCl_3$) 1.32 (t, 3 H), 4.30 (q, 2 H), 6.02 (q, 2 H), 6.69 (d, 1 H), and 7.1—7.7 (m, 4 H).

2-*Ethoxy*-1-*ethoxycarbonyl*-1,2,3,4-*tetrahydroquinoline* (10). EEDQ (1.0 g, 0.004 mol) was dissolved in ethanol (100 ml) and platinum oxide (0.2 g) was added. The mixture was hydrogenated at room temperature for 12 h at 55 p.s.i. The platinum oxide was filtered off and evaporation of the ethanol *in vacuo* gave the tetrahydroquinoline (10) as an oily liquid (Found: C, 67.3; H, 7.9; N, 6.0. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.6; N, 5.6%); $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ($CDCl_3$) 1.16 (m, 6 H), 2.02 (m, 2 H), 2.75 (m, 2 H), 3.53 (q, 2 H), 4.18 (q, 2 H), 5.81 (t, 1 H), and 6.95—7.58 (m, 4 H).

The following materials were prepared by the general method of ref. 28; the product in each case was an oil which microanalysis and n.m.r. showed to consist of a 1 : 1 mixture of the dihydroquinoline and quinoline. Conventional separation techniques were unsuccessful in separating the components without decomposition of the dihydroquinolines. 1-Ethoxycarbonyl-2-methoxy-1,2-dihydroquinoline (12, R = Me), $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ($CDCl_3$) 1.15 (t, 3 H), 3.19 (s, 3 H), 4.06 (q, 2 H), 5.92 (q, 2 H), 6.5 (m, 1 H), and 6.9—7.8 (m, ArH). 2-Ethoxy-1-phenoxycarbonyl-1,2-dihydroquinoline (14), $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ($CDCl_3$) 1.10 (t, 3 H), 3.69 (q, 2 H), 6.08 (m, 2 H), 6.61 (d, 1 H), and 6.94—7.52 (m, ArH). 1-Ethoxy-2-ethoxycarbonyl-1,2-dihydroisoquinoline (13), $\nu_{max.}$ 1 720 cm^{-1} (C=O); δ($CDCl_3$) 1.18 (dt, 6 H), 3.53 (q, 2 H), 4.24 (q, 2 H), 5.93 (d, 2 H), 6.46 (s, 1 H), and 6.95—7.83 (m, ArH).

Kinetic Measurement.—The kinetics of hydrolysis of the 1,2-dihydroquinolines were followed on a Cary 14 u.v. spectrophotometer. The pH of the solution was maintained by the use of a pH-stat assembly described elsewhere.[27] In some cases at sufficiently low pH values, *i.e.* below *ca.* 2.5, where addition of buffer was unnecessary the kinetics of hydrolysis were followed on a Unicam SP 800 u.v. spectrophotometer. In these cases the pH was measured by a glass electrode (Metrohm EA 125U), standardized in aqueous solution at 25 °C by use of commercial (Radiometer) buffer solutions and a Radiometer pH-meter (PHM 26). The pH was checked before and after each kinetic run. Rate constants were obtained either graphically or by use of a special least-squares programme written for the Olivetti Programma 101, and are accurate to ±3%.

Crystallographic Analysis of EEDQ.—Suitable specimens were recrystallised from light petroleum (b.p. 60—80 °C). Oscillation and Weissenberg photographs were taken to establish unit-cell dimensions and space group. For intensity measurement a crystal of dimensions *ca.* 0.4 × 0.3 × 0.2 mm^3 was mounted on an automatic, computer-controlled diffractometer. Unit-cell dimensions were refined by a least-squares fit on the positions of 23 peaks found from the diffractometer. Intensity data were collected with Mo-K_α radiation for $2\theta \leqslant 50°$ by use of an ω—2θ scan. Of 2 294 independent reflections measured, 1 490 having $I > 3.0\sigma(I)$ were considered observed and used in the subsequent structure refinement. No absorption corrections were made. Data reduction and subsequent crystallographic calculations were performed using the 'CRYSTALS' system of programs.[30] Atomic scattering factors were taken from ref. 31.

TABLE 8

Atom co-ordinates for EEDQ, compound (1), with their standard deviations in parentheses; hydrogen atoms are numbered according to the atom to which they are bonded

Atom	*x/a*	*y/b*	*z/c*
N(1)	0.215 2(2)	0.127 3(3)	0.505 4(2)
C(2)	0.325 8(2)	0.062 6(4)	0.516 9(2)
C(3)	0.386 5(3)	0.152 3(4)	0.446 9(3)
C(4)	0.336 5(3)	0.216 8(4)	0.363 0(3)
C(5)	0.220 9(3)	0.199 3(4)	0.335 3(2)
C(6)	0.169 1(3)	0.225 9(5)	0.238 5(2)
C(7)	0.060 6(3)	0.201 7(5)	0.214 0(3)
C(8)	0.001 0(3)	0.151 8(5)	0.285 3(3)
C(9)	0.050 1(3)	0.126 2(4)	0.381 9(2)
C(10)	0.159 8(2)	0.151 0(4)	0.407 1(2)
C(11)	0.180 9(2)	0.186 9(4)	0.589 6(2)
O(12)	0.229 0(2)	0.166 9(3)	0.671 9(2)
O(13)	0.088 3(2)	0.272 3(3)	0.569 4(2)
C(14)	0.045 6(3)	0.341 5(7)	0.654 5(3)
C(15)	−0.067 7(4)	0.387 0(6)	0.620 3(4)
O(16)	0.329 3(2)	−0.119 8(3)	0.499 1(2)
C(17)	0.296 1(4)	−0.223 7(5)	0.575 6(3)
C(18)	0.326 8(4)	−0.411 1(6)	0.560 4(4)
H(2)	0.356(2)	0.078(4)	0.586(2)
H(3)	0.468(3)	0.145(4)	0.474(2)
H(4)	0.382(3)	0.280(4)	0.319(2)
H(6)	0.213(3)	0.265(5)	0.190(3)
H(7)	0.028(3)	0.224(5)	0.144(3)
H(8)	−0.077(3)	0.132(5)	0.272(3)
H(9)	0.009(2)	0.090(4)	0.435(2)
H(14A)	0.084(3)	0.454(5)	0.666(3)
H(14B)	0.053(4)	0.244(7)	0.710(4)
H(15A)	−0.096(4)	0.451(6)	0.679(3)
H(15B)	−0.071(4)	0.473(7)	0.557(4)
H(15C)	−0.114(5)	0.277(8)	0.599(4)
H(17A)	0.322(3)	−0.178(5)	0.637(3)
H(17B)	0.224(4)	−0.210(6)	0.575(3)
H(18A)	0.289(3)	−0.447(6)	0.499(3)
H(18B)	0.305(3)	−0.478(7)	0.612(3)
H(18C)	0.413(5)	−0.411(7)	0.558(4)

Crystal Data.—$C_{14}H_{17}NO_3$, M = 247.284. Monoclinic, a = 12.608(2), b = 7.644(1), c = 13.734(2) Å, β = 99.06(2)°, U = 1 307.11 $Å^3$, Z = 4, D_c = 1.26 g cm^{-3}, $F(000)$ = 528. Space group $P2_1/n$ uniquely from systematic absences. Mo-K_α radiation, λ = 0.710 69 Å, μ(Mo-K_α) = 0.95 cm^{-1}.

The structure was solved by direct methods by use of the MULTAN program.[32] 150 Reflections with $E > 1.85$ were used and the best set of phases produced had a figure-of-merit 1.200 2. A subsequent E map based on these phases revealed all non-hydrogen atom positions, with the

exception of one terminal carbon of an ethyl group, as the 17 largest peaks in the map. A structure-factor calculation on these positions, followed by a difference map revealed the position of the missing atom as the only feature in the map. Four cycles of full-matrix least-squares refinement of atomic positions and isotropic temperature factors lowered the value of R from 0.263 to 0.126. In subsequent calculations the atoms were allowed to vibrate anisotropically. After apparent convergence with agreement factor R 0.095, a difference-Fourier synthesis was calculated which revealed the positions of all 17 hydrogen atoms. Hydrogen atoms were then included in the refinement with isotropic temperature factors. Analysis of the agreement of F_o and F_c suggested the adoption of a weighting scheme based on a Chebyshev polynomial. Further refinement finally converged when the largest parameter shifts were $< 0.5\ \delta$, lowering R to a final value of 0.0547 after a total of 13 cycles of refinement. A final difference map was calculated which showed no peaks or depressions >0.2 eÅ^{-3}. Final atomic co-ordinates are listed in Table 7; temperature factors and observed and calculated structure factors are listed in Supplementary Publication No. SUP 22588 (17 pp.).*

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

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