

1,3-Dipolar Cycloaddition Reaction of 3,4-Dihydro-6,7-dimethoxyisoquinoline Ylide with Olefins

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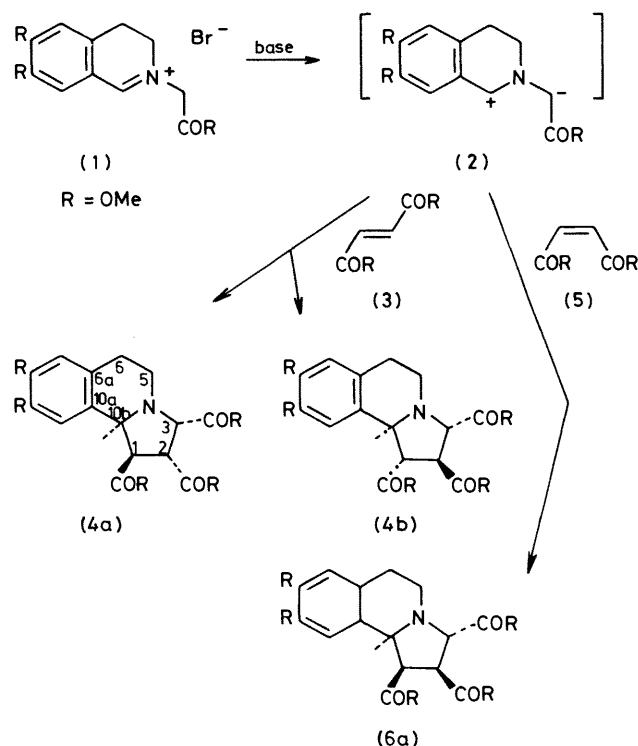
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2-Methoxycarbonylmethyl-3,4-dihydro-6,7-dimethoxyisoquinolinium ylide (2) in a concerted cycloaddition reaction of type $\pi_{4s} + \pi_{2s}$ with dimethyl fumarate and dimethyl maleate gives the (4a) 'endo', (4b) 'exo', and (6a) 'endo'-pyrrolo[2,1-a]isoquinoline derivatives, respectively. The structure and conformation of the products have been determined by ^1H , ^{13}C , and ^{15}N n.m.r. spectroscopy and X-ray diffraction for compound (4a).

Earlier we reported that the reactions of 3,4-dihydro-6,7-dialkoxyisoquinoline ylides and azomethines led to the formation of imidazo[2,1-a]isoquinoline derivatives with a diastereoselectivity depending on the structures of the dipolarophiles.^{1,2} Although a large number of 1,3-dipolar cycloadditions³ have been studied, a few even involving addition of 3,4-dihydroisoquinoline N-ylides to a variety of dipolarophiles,⁴ the stereochemistry of the products was unknown. In recent years however several reports have dealt with the diastereoselectivity of the cycloadditions of maleic and fumaric esters to various 1,3-dipoles.⁵⁻⁷ We now report results for the cycloaddition of dimethyl fumarate (3) and dimethyl maleate (5) to the ylide (2) generated *in situ* from the appropriate quaternary isoquinolinium salt (1). On the basis of the structure determination of the products we have rationalized the stereoselectivity of the cycloadditions with respect to the reaction mechanism.

The results of the preparative experiments showed that the reaction of (2) and (3) resulted in formation of (4a) *endo*- and (4b) *exo*-isomers whilst the reaction of (2) and (5) gave the *endo*-isomer (6a) exclusively. The ^1H n.m.r. spectra of reactions carried out in n.m.r. sample tubes showed that (4a) and (4b) were formed in a ratio of 4 : 1, further confirmation that the hypothetical *exo* isomer (6b) was not formed and that the two reactions gave different products. In view of the latter observations, the cycloadditions are to be interpreted as processes of a pure concerted mechanism. In the transition state leading to the formation of (4b) no steric hindrance occurs between R^2 and the ester moiety ($\text{R}^2 = \text{H}$), nevertheless (4a) is formed as the major product as a consequence of the attractive π overlap between R^4 (CO_2Me) and the aromatic ring, which outweighs the steric repulsion ($\text{R}^2 = \text{CO}_2\text{Me}$). The transition state leading to the exclusive formation of (6a; $\text{R}^1, \text{R}^4 = \text{CO}_2\text{Me}$) is favourable not only sterically, but also in respect of the secondary π overlap.

Structure Elucidation.—The determination of structure was based on an X-ray study of (4a) coupled with comparative ^1H , ^{13}C , and ^{15}N n.m.r. analyses to determine the configurations and conformations of the products (4a), (4b), and (6a). The structural problem was particularly challenging since the resulting pyrroloisoquinolines besides possessing four centres of chirality, also incorporate a bridgehead nitrogen in a relatively flexible skeleton; thus, ring and nitrogen inversions have also to be considered when describing the conformations. For the junction of the six-membered *b* and the five-membered *c* ring, a ternary conformational equilibrium must also be



Scheme 1.

taken into account. Inversion of the nitrogen atom for the *trans* *b/c* ring fusion conformer leads to the *cis*-1 conformer in which the C-3 atom is axial with respect to the *b* ring. Ring inversion for the *cis*-1 conformer results in formation of a *cis*-2 conformer in which, however, the C-1 atom occupies the axial position.⁸ The pseudorotation of the five-membered ring renders possible the coexistence of several conformations at the *c* ring.

The molecular diagram of (4a), based on the X-ray analysis, is shown in Figure 2 together with the atomic numbering. Selected torsion angles, also those related to the generated lone pair of N-4 are summarized in Table I. The conformation of the molecule in the solid phase can be described by four planes: P1, formed by the atoms of the benzene ring, and the P2, P3, and P4 planes formed by the individual methoxy-

Table 1. Selected torsion angles in (4a). E.s.d.'s are in the range of 0.05°

| | | | |
|--------------------------|--------|--------------------------|--------|
| C(3)-N(4)-C(10b)-C(1) | 32.7° | N(4)-C(3)-C(2)-C(1) | 29.5° |
| N(4)-C(10b)-C(1)-C(2) | -14.0 | C(5)-N(4)-C(3)-C(2) | 81.9 |
| C(5)-N(4)-C(10b)-C(1) | -86.6 | C(6)-C(5)-N(4)-C(3) | -179.3 |
| C(6a)-C(6)-C(5)-N(4) | 53.4 | C(6a)-C(10a)-C(10b)-C(1) | 112.1 |
| C(6a)-C(10a)-C(10b)-N(4) | -11.6 | C(7)-C(6a)-C(6)-C(5) | 155.1 |
| C(10)-C(10a)-C(10b)-C(1) | -66.6 | C(10)-C(10a)-C(10b)-N(4) | 169.8 |
| C(10a)-C(6a)-C(6)-C(5) | -24.6 | C(10a)-C(10b)-C(1)-C(2) | -141.5 |
| C(10a)-C(10b)-N(4)-C(3) | 160.7 | C(10a)-C(10b)-N(4)-C(5) | 41.4 |
| C(10b)-C(1)-C(2)-C(3) | -9.2 | C(10b)-N(4)-C(3)-C(2) | -38.8 |
| C(10b)-N(4)-C(5)-C(6) | -63.2 | C(14)-C(1)-C(2)-C(3) | -131.2 |
| C(14)-C(1)-C(10b)-C(10a) | -19.1 | O(15)-C(14)-C(1)-C(2) | 39.2 |
| C(18)-C(2)-C(1)-C(10b) | -137.2 | C(18)-C(2)-C(1)-C(14) | 100.8 |
| C(18)-C(2)-C(3)-N(4) | 156.7 | O(19)-C(18)-C(2)-C(1) | -21.1 |
| C(22)-C(3)-C(2)-C(1) | -88.3 | C(22)-C(3)-C(2)-C(18) | 38.9 |
| C(22)-C(3)-N(4)-C(5) | -157.8 | C(22)-C(3)-N(4)-C(10b) | 81.5 |
| O(23)-C(22)-C(3)-C(2) | 29.7 | H(2)-C(2)-C(1)-H(1) | -123.9 |
| H(3)-C(3)-C(2)-H(2) | 34.1 | H(61)-C(6)-C(5)-H(51) | -57.9 |
| H(61)-C(6)-C(5)-H(52) | 57.0 | H(62)-C(6)-C(5)-H(51) | 44.2 |
| H(62)-C(6)-C(5)-H(52) | 159.1 | E(4)*-N(4)-C(3)-H(3) | 68.0 |
| E(4)-N(4)-C(5)-H(51) | -75.1 | E(4)-N(4)-C(5)-H(52) | 174.6 |
| E(4)-N(4)-C(10b)-H(10b) | 39.8 | | |

* The position of the lone pair electron of the N(4) atom, E(4) was generated assuming tetrahedral geometry.

Table 2. Least-squares planes of (4a) in the form $AX + BY + CZ + D = 0$, whereas A, B, C, and D are constants and X, Y, and Z are orthogonalized co-ordinates

$$P1 \ A = 0.6034 \ B = -0.7636 \ C = -0.2296 \ D = 2.3466$$

Atoms forming the plane

| Atom | Distance | Atom | Distance |
|-------|----------|--------|----------|
| C(6a) | 0.006 Å | C(9) | 0.000 Å |
| C(7) | 0.011 | C(10) | 0.016 |
| C(8) | -0.013 | C(10a) | -0.019 |

Atoms not forming the plane

| Atom | Distance | Atom | Distance |
|--------|----------|-------|----------|
| C(6) | 0.021 Å | C(27) | -0.272 Å |
| C(10b) | -0.115 | O(28) | 0.007 |
| C(26) | -0.058 | C(29) | -0.186 |

$$P2 \ A = -0.1315 \ B = 0.9079 \ C = -0.3980 \ D = 7.0925$$

Atoms forming the plane

| Atom | Distance | Atom | Distance |
|-------|----------|-------|----------|
| C(1) | -0.022 | O(16) | 0.032 |
| C(14) | 0.013 | C(17) | -0.026 |
| O(15) | 0.003 | | |

$$P3 \ A = 0.8845 \ B = -0.4481 \ C = -0.1301 \ D = -1.2828$$

Atoms forming the plane

| Atom | Distance | Atom | Distance |
|-------|----------|-------|----------|
| C(2) | 0.026 | O(20) | -0.044 |
| C(18) | -0.008 | C(21) | 0.034 |
| C(19) | -0.008 | | |

$$P4 \ A = -0.2783 \ B = 0.7923 \ C = -0.5430 \ D = 9.7109$$

Atoms forming the plane

| Atom | Distance | Atom | Distance |
|-------|----------|-------|----------|
| C(3) | -0.006 | C(24) | 0.001 |
| C(22) | 0.012 | C(25) | -0.004 |
| C(23) | -0.004 | | |

Dihedral angles between planes

| | | | |
|--------|--------|--------|--------|
| P1, P2 | -47.1° | P1, P2 | -50° |
| P2, P3 | -61.9° | P2, P3 | -58.0° |

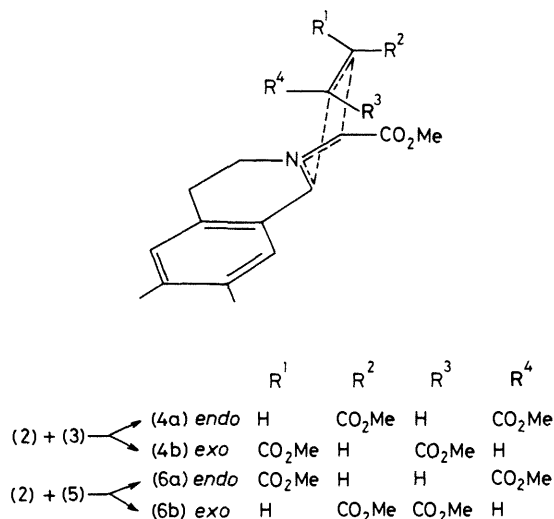
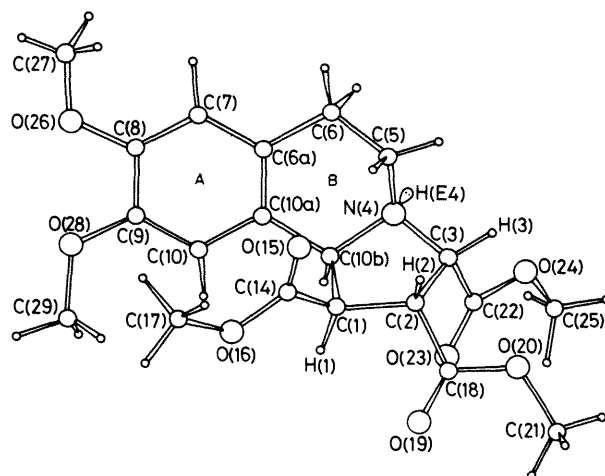
**Scheme 2.****Figure 1.** Molecular diagram of (4a) based on its X-ray analysis. E-4 indicates the lone pair on the N-4 atom

Table 3. ^1H , ^{13}C , and ^{15}N N.m.r. chemical shifts ^a and $^3J_{\text{H,H}}$ or $^1J_{\text{C,H}}$ coupling constants (Hz) of compounds (4a), (4b), and (6a) taken in CDCl_3

| | (4a) | | | | (4b) | | | | (6a) | | | |
|-------------------|------------------------------|-----------------------------|---------------------------------|-----------------------------|------------------------------|-----------------------------|---------------------------------|-----------------------------|------------------------------|-----------------------------|---------------------------------|-----------------------------|
| | ^1H δ (J) | $\Delta\delta$ ^b | ^{13}C δ (J) | ^{15}N δ | ^1H δ (J) | $\Delta\delta$ ^b | ^{13}C δ (J) | ^{15}N δ | ^1H δ (J) | $\Delta\delta$ ^b | ^{13}C δ (J) | ^{15}N δ |
| 1 | 4.02 | | 50.9 ^c | | ≈ 4.0 | | 52.8 ^c | | 3.70— 4.05 | | 51.3 ^c | |
| 2 | 3.90 | | 49.0 ^c | | 3.70— 4.10 | | 50.1 ^c | | | | 48.9 ^c | |
| 3 | 4.32 (7.93 Hz) | 0.74 | 69.1 (149.5 Hz) | | | ≈ 1.0 | 65.7 (141.0 Hz) ^c | | 4.39 (8.54 Hz) | 0.63 | 66.4 ^d (147.1 Hz) | |
| 4 | | | | -323.4 | | | | -329.4 | | | | -332.0 |
| 5 | } 2.65— 3.30 | | 46.6 | | } 2.65— 3.30 | | 45.2 | | } 2.55— 3.45 | | 46.2 | |
| 6 | | | 47.8 | | | | 24.1 | | | 27.2 | | |
| 6a | | | 124.2 | | | | 125.7 | | | | 124.9 | |
| 7 | 6.58 | | 110.7 | | 6.52 | | 110.9 | | 6.58 | | 110.8 | |
| 8 | | | 147.5 | | | | 147.5 | | | | 147.4 | |
| 9 | | | 146.6 | | | | 147.2 | | | | 146.8 | |
| 10 | 6.65 | | 110.1 | | 6.62 | | 108.8 | | 6.64 | | 110.2 | |
| 10a | | | 126.9 | | | | 126.8 | | | | 128.4 | |
| 10b | 4.90 (9.16 Hz) | 0.85 | 62.9 (145.5 Hz) | | 4.65 (6.5 Hz) | 0.73 | 64.0 (145.3 Hz) ^e | | 4.83 (6.11 Hz) | 0.85 | 62.8 (144.5 Hz) | |
| CH ₃ O | 3.87 | | 55.6 | | 3.82 | | 55.2 | | 3.85 | | 55.6 | |
| | 3.88 | | 55.6 | | 3.82 | | 55.2 | | 3.86 | | 55.8 | |
| | | | 170.9 | | | | 171.4 | | | | 170.6 | |
| C=O | | | 171.4 | | | | 171.4 | | | | 172.1 | |
| | | | 173.7 | | | | 172.4 | | | | 173.4 | |
| | 3.40 | | 51.6 | | 3.63 | | 51.2 | | 3.27 | | 51.3 | |
| OCH ₃ | 3.73 | | 51.6 | | 3.80 | | 51.2 | | 3.67 | | 52.2 | |
| | 3.77 | | 52.1 | | 3.80 | | 51.6 | | 3.82 | | 52.2 | |

^a ^1H , ^{13}C $\delta(\text{SiMe}_4) = 0$ p.p.m.; ^{15}N $\delta(\text{CH}_3\text{NO}_2) = 0$ p.p.m., upfield shifts from the standard are negative. ^b Protonation shift. ^c Values may be pairwise interchanged. ^d Assignment provided by selective $^{13}\text{C}\{^1\text{H}\}$ experiment. ^e Measured by selective excitation DANTE method.

carbonyl groups (see Table 2). The six-membered ν ring with the Cremer-Pople puckering parameters⁹ of $Q = 0.49$ Å, $\theta = 132^\circ$, $\varphi = 135^\circ$ [numbering sequence N(4)-C(10b)-C(10a)-C(6a)-C(6)-C(5),] has a conformation midway between a 6E envelope ($\theta = 125^\circ$, $\varphi = 120^\circ$) and a $^6\text{H}_1$ half-chair ($\theta = 129^\circ$, $\varphi = 150^\circ$). The nomenclature of the canonical conformations is given in ref. 10. The conformation of the ϵ ring with the Cremer-Pople puckering parameters of $Q = 0.36$ Å and $\varphi = 15^\circ$ is close to the ideal 1T_2 ($\varphi = 18^\circ$) twist conformation¹¹ [numbering sequence N(4)-C(3)-C(2)-C(1)-C(10b)]. Endocyclic torsion angles indicate that the ν/ϵ ring junction is of the *cis*-2 type with C-1 in the axial position to the ν ring and C-5 axial to the ϵ ring; furthermore, C-22 lies in an axial, C-14 in an isoclinal, and C-18 in an equatorial position.

In the ^1H n.m.r. spectra the signals of 10b-H and 3-H, however close to each other, give the most useful information concerning the structure and conformation (Table 3). The verification of the allyl coupling of *ca.* 1 Hz between 10b-H and 10-H protons by a double resonance experiment gave support for the assignment. Using the modified Karplus equation and also taking into account the electronegativity of the substituents¹² we have got for the possible dihedral angles between bonds 10b-H:1-H and 3-H:2-H the following values, respectively: (4a) 16° or 156° and 33° or 146° , (4b) 140° or 40° ; the other pair of values could not be calculated, (6a) 140° or 37° and 151° or 31° .

It is known that if the lone pair of the nitrogen atom is in an antiperiplanar position to the proton on an adjacent carbon atom then an upfield shift of *ca.* 0.5 p.p.m. is observed for the proton signal.¹³ Accordingly, with such a spatial arrangement, the downfield shift caused by protonation of the nitrogen atom is significantly greater (*ca.* 1 p.p.m.) than normal.¹⁴ The 'protonation shift' values measured for the signals of 10b-H and 3-H on adding trifluoroacetic acid to the CDCl_3 solution

are shown in Table 3. Although in the case of (4b) the addition of acid was the only way for the 3-H signal to be observed separately, the large protonation shift of *ca.* 1 p.p.m. is indicative of an antiperiplanar arrangement of 3-H and the lone pair. The values of 0.6–0.7 p.p.m. found at (4a) and (6a) suggest a *gauche* arrangement. These values measured on the 10b-H signal were 0.73 p.p.m. for (4b) and 0.85 p.p.m. for (4a) and (6a) which indicates that the dihedral angles are less than 180° .

In the ^{13}C n.m.r. signal assignment we utilized the broad band proton-decoupled and proton-coupled spectra, the known additivity rules,¹⁵ and the assignments for analogous compounds.^{1,8,16,17} The C-10b, C-5, and C-6 signals for ring ν in compounds (4a) and (6a) establishes that the ν/ϵ ring fusion is identical in the two compounds. Since the measured chemical shifts (27.8 and 27.2 p.p.m.) for C-6 indicate that there is no carbon atom in a γ -*gauche* position with respect to it, the ring fusion may be either *trans*- or *cis*-2.²⁰ In the *cis*-2 conformation a γ -*gauche* steric interaction would operate between the C-1 and C-5 atoms but no upfield shift has been found for the C-5 signal; we thus concluded that the ν/ϵ ring junction was *trans*. For the (4b) isomer, however, C-6 and C-3 are in a γ -*gauche* relationship as indicated by the pronounced upfield shift of the corresponding signals; this establishes the *cis*-1 character of the ν/ϵ ring junction.

All the above discussed spectroscopic results show that for the ϵ ring of (4a) an envelope-like conformer may predominate, so that the C-3 atom protrudes from the plane; further, because of the axial position of the adjoining ester group, there is a slight γ -*gauche* effect with respect to the C-10b and C-1. In the corresponding *exo* (4b) isomer C-3 is on top of the envelope, but since the ester group is quasi-equatorial the former γ -*gauche* interaction no longer exists. In the isomer (6a) C-10b protrudes from the plane and the

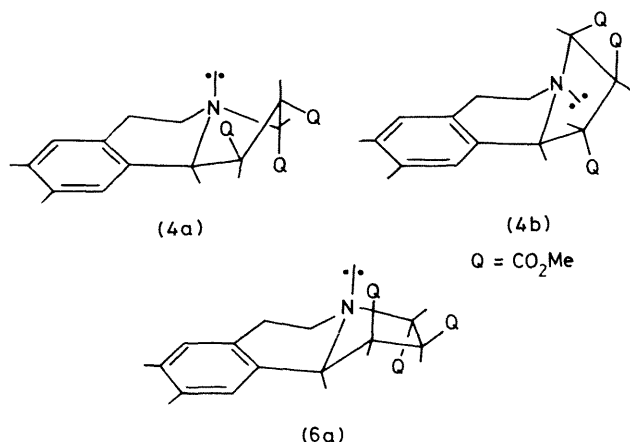


Figure 2. Predominating conformers of compounds (4a), (4b), and (6a) in solution

ester group adjacent to C-1 gives rise to a γ -gauche interaction with N-4 and C-3. The -2.7 p.p.m. upfield shift of the C-3 signal compared with that in (4a) is a result of this interaction.

In order to confirm the above deduced structures and predominant conformations we have also determined the $^1J_{C,H}$ coupling constants on the angular carbon atoms adjacent to N-4. It is known that the orientation of the lone pair of the nitrogen atom has a specific influence on the $^1J_{C,H}$ coupling constants and this can be utilized for the determination of the relative configuration of the angular hydrogens and of the lone pair.¹⁷ In case of an antiperiplanar arrangement the $^1J_{C,H}$ coupling constant is 6–10 Hz lower than in the case of synclinal configuration.^{21,22} From the data of Table 3 it becomes clear that only in compound (4b) are 3-H and the lone pair of the nitrogen atom antiperiplanar (141.0 Hz), whereas in (4a) and (6a) they are synclinal (149.5 and 147.1 Hz, respectively).

The values of $^1J_{C(10b),H(10b)}$ are very close to each other (144.5–145.5 Hz) and found between the two former values. These results show that in none of the compounds is a pronounced *trans* antiperiplanar arrangement established between 10b-H and the lone pair. It should be noted that the individual coupling constants could be directly read from the corresponding proton-coupled ^{13}C n.m.r. spectrum in compounds (4a) and (6a). For (4b), however, in order to avoid the disadvantageous signal overlappings the coupling constants have been determined by using the DANTE method for selective excitation.^{18,19}

The ^{15}N n.m.r. investigations gave further proof of the proposed structures. Changing the orientation of a γ -substituent from equatorial to axial results in shielding of ca. -10 p.p.m. as a result of a γ -gauche steric effect being established.^{23–25} In nitrogen bridgehead compounds the ^{15}N chemical shift sensitivity reflects the *trans* or *cis* character of the ring fusion as well, a significant upfield shift being observed for the nitrogen signal in the latter case.²³ The -323.4 p.p.m. value measured in (4a) is characteristic for *trans* fusion of the B/C rings; further, its good agreement with the results of Lichter²³ establishes that none of the C ring substituents take part in a γ -gauche steric interaction. The upfield shift found in (4b) clearly shows the *cis* B/C ring fusion. In compound (6a) shielding of 10 p.p.m. has been found for the N atom compared with that for (4c). This is in agreement with the 1-CO₂Et group being involved in a strong γ -gauche interaction with N-4. A similar, though smaller effect is

Table 4. Fractional co-ordinates of (4a), estimated standard deviations are in parentheses

| | X/a | Y/b | Z/c | B _{eq} |
|--------|-------------|-------------|-------------|-----------------|
| C(1) | -0.376 8(5) | 0.091 3(2) | -0.589 2(1) | 3.06(11) |
| C(2) | -0.494 8(6) | 0.107 8(2) | -0.646 2(1) | 3.24(12) |
| C(3) | -0.470 5(5) | 0.017 6(2) | -0.678 9(1) | 3.14(11) |
| N(4) | -0.465 1(4) | -0.053 8(2) | -0.635 5(1) | 3.04(9) |
| C(5) | -0.701 9(5) | -0.076 3(2) | -0.617 5(1) | 3.43(12) |
| C(6) | -0.694 0(6) | -0.149 3(2) | -0.572 3(1) | 3.48(12) |
| C(6a) | -0.539 4(5) | -0.122 8(2) | -0.524 7(1) | 3.06(11) |
| C(7) | -0.571 5(6) | -0.159 4(2) | -0.470 7(1) | 3.61(13) |
| C(8) | -0.431 1(6) | -0.134 9(2) | -0.426 6(1) | 3.60(12) |
| C(9) | -0.246 9(6) | -0.074 3(2) | -0.436 0(1) | 3.44(12) |
| C(10) | -0.211 4(5) | -0.039 1(2) | -0.488 9(1) | 3.32(12) |
| C(10a) | -0.362 4(5) | -0.061 4(2) | -0.533 5(1) | 2.79(11) |
| C(10b) | -0.327 9(5) | -0.015 1(2) | -0.589 4(1) | 2.88(11) |
| C(14) | -0.522 5(6) | 0.120 7(2) | -0.539 4(1) | 3.73(13) |
| O(15) | -0.729 0(4) | 0.110 7(2) | -0.535 9(1) | 5.04(11) |
| O(16) | -0.391 1(4) | 0.157 6(1) | -0.499 8(1) | 4.30(10) |
| C(17) | -0.505 1(8) | 0.183 6(2) | -0.447 6(1) | 5.46(17) |
| C(18) | -0.412 4(7) | 0.191 0(2) | -0.676 6(1) | 4.09(14) |
| O(19) | -0.317 5(6) | 0.254 8(1) | -0.655 4(1) | 7.34(14) |
| O(20) | -0.458 0(4) | 0.186 6(1) | -0.731 2(1) | 4.35(10) |
| C(21) | -0.370 6(9) | 0.258 9(2) | -0.766 1(1) | 5.84(18) |
| C(22) | -0.247 6(6) | 0.013 1(2) | -0.712 3(1) | 3.48(12) |
| O(23) | -0.070 0(4) | 0.050 4(2) | -0.699 5(1) | 5.18(11) |
| O(24) | -0.270 4(4) | -0.040 3(1) | -0.757 0(1) | 4.98(11) |
| C(25) | -0.070 2(8) | -0.051 9(3) | -0.792 3(1) | 6.82(20) |
| O(26) | -0.454 4(4) | -0.164 5(2) | -0.372 0(1) | 4.74(10) |
| C(27) | -0.653 2(7) | -0.214 1(3) | -0.358 1(1) | 6.09(18) |
| C(28) | -0.112 6(4) | -0.055 6(2) | -0.389 7(1) | 4.86(10) |
| C(29) | 0.052 1(7) | 0.015 3(3) | -0.395 0(1) | 5.31(17) |
| H(1) | -0.2500 | 0.1250 | -0.5820 | 3.95 |
| H(2) | -0.6680 | 0.1250 | -0.6406 | 4.17 |
| H(3) | -0.5820 | 0.0000 | -0.7090 | 4.05 |
| H(51) | -0.7910 | -0.0840 | -0.6543 | 4.38 |
| H(52) | -0.7930 | -0.0195 | -0.5977 | 4.38 |
| H(61) | -0.8750 | -0.1680 | -0.5566 | 4.54 |
| H(62) | -0.6660 | -0.2090 | -0.5977 | 4.54 |
| H(7) | -0.7070 | -0.2090 | -0.4590 | 4.56 |
| H(10) | -0.0840 | 0.0000 | -0.5000 | 4.22 |
| H(10b) | -0.1680 | -0.0215 | -0.5957 | 3.80 |
| H(170) | -0.6680 | 0.2090 | -0.4590 | 5.91 |
| H(171) | -0.5275 | 0.1272 | -0.4193 | 5.91 |
| H(172) | -0.4115 | 0.2356 | -0.4241 | 5.91 |
| H(210) | -0.3750 | 0.2285 | -0.8047 | 6.41 |
| H(211) | -0.4590 | 0.3125 | -0.7656 | 6.41 |
| H(212) | -0.2039 | 0.2872 | -0.7540 | 6.41 |
| H(250) | 0.0430 | -0.1055 | -0.7793 | 7.34 |
| H(251) | -0.1116 | -0.0649 | -0.8350 | 7.34 |
| H(252) | 0.0401 | 0.0089 | -0.7897 | 7.34 |
| H(270) | -0.7910 | -0.1875 | -0.3750 | 6.73 |
| H(271) | -0.6660 | -0.2305 | -0.3203 | 6.73 |
| H(272) | -0.6594 | -0.2805 | -0.3786 | 6.73 |
| H(290) | 0.0000 | 0.0625 | -0.4180 | 6.13 |
| H(291) | 0.0917 | 0.0444 | -0.3544 | 6.13 |
| H(292) | 0.2094 | -0.0100 | -0.4141 | 6.13 |

expected—owing to the greater spatial distance—as a result of the interaction of the 2-CO₂Et group.

It should be noted that as in the case of alkaloids²³ a remarkable nuclear Overhauser effect has been found owing to the relatively large molecular size; this implies a longer relaxation time. This, and the high solubility of the compounds, made it possible to obtain ^{15}N n.m.r. spectra with an appropriate S:N ratio at natural abundance within an acceptable time (1–2 h).

In conclusion, we have found that compound (4a) in the solid phase exists in a *cis*-2 conformation, whereas in chloroform the *trans* conformer is preferred.

Table 5. Bond distances (Å) and angles (°) for (4a)

| Bond lengths (Å) with e.s.d.'s | | Bond angles (°) with e.s.d.'s | |
|--------------------------------|----------|-------------------------------|----------|
| C(1)–C(2) | 1.533(4) | C(2)–C(1)–C(10b) | 103.5(4) |
| C(1)–C(10b) | 1.594(4) | C(2)–C(1)–C(14) | 113.1(4) |
| C(1)–C(14) | 1.516(4) | C(2)–C(1)–H(1) | 116.3(5) |
| C(1)–H(1) | 0.904(3) | C(10b)–C(1)–C(14) | 112.5(4) |
| C(2)–C(3) | 1.546(4) | C(10b)–C(1)–H(1) | 113.4(4) |
| C(2)–C(18) | 1.501(4) | C(14)–C(1)–H(1) | 98.5(4) |
| C(2)–H(2) | 1.044(3) | C(1)–C(2)–C(3) | 105.3(4) |
| C(3)–N(4) | 1.472(3) | C(1)–C(2)–C(18) | 114.3(4) |
| C(3)–O(22) | 1.518(4) | C(1)–C(2)–H(2) | 110.9(4) |
| C(3)–H(3) | 0.998(3) | C(3)–C(2)–C(18) | 115.7(4) |
| N(4)–C(5) | 1.476(4) | C(3)–C(2)–H(2) | 111.1(4) |
| N(4)–C(10b) | 1.468(3) | C(18)–C(2)–H(2) | 99.7(4) |
| C(5)–C(6) | 1.520(4) | C(2)–C(3)–N(4) | 105.5(4) |
| C(5)–H(51) | 1.020(3) | C(2)–C(3)–O(22) | 112.2(4) |
| C(10a)–C(10b) | 1.505(4) | C(2)–C(3)–H(3) | 121.5(4) |
| C(10b)–H(10b) | 0.944(3) | N(4)–C(3)–C(22) | 108.4(4) |
| C(14)–O(15) | 1.209(4) | N(4)–C(3)–H(3) | 109.1(4) |
| C(14)–O(16) | 1.325(4) | C(22)–C(3)–H(3) | 99.6(4) |
| O(16)–C(17) | 1.456(4) | C(3)–N(4)–C(5) | 110.1(4) |
| C(17)–H(170) | 1.052(4) | C(3)–N(4)–C(10b) | 104.7(4) |
| C(17)–H(171) | 1.076(3) | C(3)–N(4)–H(E4) | 113.1(4) |
| C(17)–H(172) | 1.091(4) | C(5)–N(4)–C(10b) | 112.1(4) |
| C(18)–C(19) | 1.199(4) | C(5)–N(4)–H(E4) | 105.9(4) |
| C(18)–O(20) | 1.323(3) | C(10b)–N(4)–H(E4) | 111.1(4) |
| O(20)–C(21) | 1.442(4) | N(4)–C(6)–C(6) | 109.6(4) |
| C(21)–H(210) | 1.018(3) | N(4)–C(5)–H(51) | 104.5(4) |
| C(21)–H(211) | 0.942(4) | N(4)–H(52)–H(52) | 113.6(4) |
| C(21)–H(212) | 1.092(5) | C(6)–C(5)–H(51) | 122.7(5) |
| C(5)–H(52) | 1.097(3) | C(6)–C(5)–H(52) | 104.6(4) |
| C(6)–C(6a) | 1.492(4) | H(51)–C(5)–H(52) | 102.0(4) |
| C(6)–H(61) | 1.147(3) | C(5)–C(6)–C(6a) | 111.5(4) |
| C(6)–H(62) | 1.079(3) | C(5)–C(6)–H(61) | 111.8(4) |
| C(6a)–C(7) | 1.403(4) | C(5)–C(6)–H(62) | 100.9(4) |
| C(6a)–C(10a) | 1.385(4) | C(6a)–C(6)–H(61) | 111.6(4) |
| C(7)–C(8) | 1.372(4) | C(6a)–C(6)–H(62) | 123.0(5) |
| C(7)–H(7) | 1.109(3) | H(61)–C(6)–H(62) | 97.0(4) |
| C(8)–C(9) | 1.410(4) | C(6)–C(6a)–C(7) | 120.7(4) |
| C(8)–O(26) | 1.373(3) | | |
| C(9)–C(10) | 1.374(4) | | |
| C(9)–O(28) | 1.373(4) | | |
| C(10)–C(10a) | 1.411(4) | | |
| C(10)–H(10) | 0.974(3) | | |
| C(22)–O(23) | 1.206(4) | | |
| C(22)–O(24) | 1.326(3) | | |
| O(24)–C(25) | 1.441(5) | | |
| C(25)–H(250) | 1.072(5) | | |
| C(25)–H(251) | 1.058(3) | | |
| C(25)–H(252) | 1.103(5) | | |
| O(26)–C(27) | 1.404(5) | | |
| C(27)–H(270) | 0.977(4) | | |
| C(27)–H(271) | 0.931(4) | | |
| C(27)–H(272) | 1.094(4) | | |
| O(28)–C(29) | 1.421(5) | | |
| C(29)–H(290) | 0.935(4) | | |
| C(29)–H(291) | 1.078(3) | | |
| C(29)–H(292) | 1.085(4) | | |
| | | C(6)–C(6a)–C(10a) | 120.2(4) |
| | | C(7)–C(6a)–C(10a) | 119.1(5) |
| | | C(6a)–C(7)–C(8) | 121.0(5) |
| | | C(6a)–C(7)–H(7) | 125.1(5) |
| | | C(8)–C(7)–H(7) | 113.8(5) |
| | | C(7)–C(8)–C(9) | 119.8(5) |
| | | C(7)–C(8)–O(26) | 125.1(5) |
| | | C(9)–C(8)–O(26) | 115.1(5) |
| | | C(8)–C(9)–C(10) | 119.7(5) |
| | | C(8)–C(9)–O(28) | 115.6(5) |
| | | C(10)–C(9)–O(28) | 124.7(5) |
| | | C(9)–C(10)–C(10a) | 120.2(5) |
| | | C(9)–C(10)–H(10) | 125.7(5) |
| | | C(10a)–C(10)–H(10) | 114.0(5) |
| | | C(6a)–C(10a)–C(10) | 120.0(4) |
| | | C(6a)–C(10a)–C(10b) | 121.9(4) |
| | | C(10)–C(10a)–C(10b) | 118.1(4) |
| | | C(1)–C(10b)–N(4) | 106.7(4) |
| | | C(1)–C(10b)–C(10a) | 114.9(4) |
| | | C(1)–C(10b)–H(10b) | 105.9(4) |
| | | N(4)–C(10b)–C(10a) | 114.1(4) |
| | | N(4)–C(10b)–H(10b) | 112.0(4) |
| | | C(10a)–C(10b)–H(10b) | 103.0(4) |
| | | C(1)–C(14)–O(15) | 124.8(5) |
| | | C(1)–C(14)–O(16) | 110.4(4) |
| | | O(15)–C(14)–O(16) | 124.8(5) |
| | | C(14)–O(16)–C(17) | 116.7(4) |
| | | C(2)–C(18)–O(19) | 125.9(5) |
| | | C(2)–C(18)–O(20) | 111.5(5) |
| | | O(19)–C(18)–C(20) | 122.7(5) |
| | | C(18)–O(20)–C(21) | 117.1(5) |
| | | C(3)–C(22)–O(23) | 125.1(5) |
| | | C(3)–C(22)–O(24) | 111.0(4) |
| | | O(23)–C(22)–O(24) | 123.8(5) |
| | | C(22)–C(24)–C(25) | 117.0(5) |
| | | C(8)–O(26)–C(27) | 117.9(4) |
| | | C(9)–O(28)–C(29) | 117.3(4) |

Experimental

Preparation of the Compounds.—The ester (1) (1.72 g, 5 mmol), pyridine (0.48 g, 6 mmol), and dimethyl fumarate (3) or dimethyl maleate (5) (0.87 g, 6 mmol) were dissolved in dichloromethane (20 cm³). The reaction mixture was then stirred at room temperature for 24 h. After removal of the solvent under reduced pressure the residue was washed with water and ether. Recrystallization of the product from ethanol afforded colourless crystals. The minor product (4b) was obtained from the ethereal washings after evaporation under reduced pressure and recrystallization from ether. Compound (4a) (1.43 g, 70%), m.p. 126–127 °C; (4b) (0.33 g, 15%), m.p. 125–126 °C; (6a) (1.75 g, 86%), m.p. 134–135 °C. The ¹H, ¹³C, and ¹⁵N n.m.r. spectra were recorded in CDCl₃ in the PFT mode (16 K data points for the FID) at 99.6, 25.0, and 10.04 MHz, respectively, with internal deuterium lock at ambient temperature using a Jeol FX-100 multinuclear spectrometer. The ¹H and ¹³C chemical shifts were determined on the δ scale using tetramethylsilane [δ(SiMe₄) = 0 p.p.m.] as internal standard. ¹⁵N Chemical shifts were measured with external aqueous K¹⁵NO₃ (δ = –3.55 p.p.m.) as reference and were converted to external neat nitromethane [δ(MeNO₂) = 0 p.p.m.]. Shifts upfield from the reference are negative. Typical acquisition parameters for determination of ¹⁵N spectra included a spectral width of 5 000 Hz, a flip angle of 30°, and a pulse delay up to 4 s.

X-Ray Analysis of (4a).—C₂₀H₂₅NO₈, *M* = 407.42. Orthorhombic, *a* = 5.799(2), *b* = 14.745(2), *c* = 23.711(2) Å, *Z* = 4, *D*_c = 1.34 g cm^{–3}, space group *P*2₁2₁2₁.

Intensities of 2 469 reflections, 2 110 with *I* ≥ 3σ(*I*) were collected on an ENRAF-NONIUS CAD4 diffractometer with graphite monochromatised Mo-*K*_α radiation. The structure was solved by direct methods and refined by full matrix least-squares procedures using the SPD structure determination package with local modification on a PDP 11/34 64 K mini-computer. Hydrogen atoms were found from a difference Fourier-map but their positions were not refined. The refinement concluded at *R* = 0.044, *R*_w = 0.055 with *w* = [σ²(*F*) + 0.01 *F*²]^{–1}. *R*_w is defined as [Σ*w*Δ²/Σ*wF*_o²]^{1/2}. Only the parameters of non-hydrogen atoms were refined. The *B*-value for the H-atoms is attached to the *i*-th atom and is *B*_{eq}(*i*) + 1.0. Fractional atomic parameters with estimated standard deviation are listed in Table 4, bond distances and angles in Table 5. Observed and calculated structure amplitudes and thermal parameters of the atoms are tabulated in Supplementary Publication No. SUP. 23597 (13 p.).*

* For details of the Supplementary publications scheme, see 'Instructions for Authors (1983)', *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

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