(*Z*)- and (*E*)-3-Alkylidene-1,3-dihydroindol-2-ones: Influence of Configuration on the Transmission of the Inductive Effect to the Carbonyl Group

By **Gianfranco Tacconi,* Lucia Dacrema Maggi, Pierpaolo Righetti,** and **Giovanni Desimoni,** Istituto di Chimica Organica dell'Università, 27100 Pavia, Italy
Ornella Azzolina and **Victor Ghislandi,** Dipartimento di Chimica Farmaceutica dell'Università, 27100 Pavia, Italy

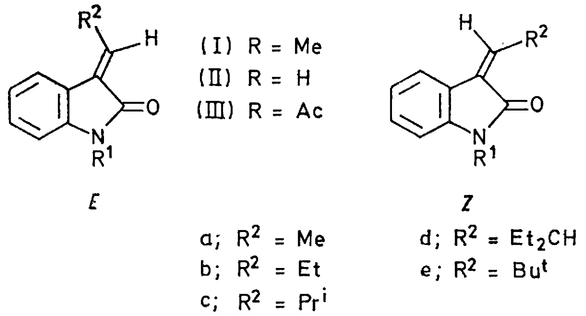
A series of (*Z*-) and (*E*-)-3-alkylidene-1,3-dihydroindol-2-ones has been prepared and their i.r. spectra in the carbonyl region recorded. Good correlations were obtained between the carbonyl stretching frequency of the *E*-isomers and the polar parameter σ^*, indicating that the inductive effect of the alkyl group is transmitted to the carbonyl group and that the variation in frequency in the series is a function of this effect only. The *Z*-isomers do not give a linear correlation and it is suggested that this is due to the steric interactions of the alkyl group with the oxygen of the carbonyl group which twists the C=C–C=O system to a certain extent with consequent variation in conjugation.

SEVERAL papers have been devoted to the transmission of electronic effects in arylidene-substituted $\alpha\beta$-unsaturated carbonyl compounds[1] in order to elucidate the effects of configuration, conformation, and ring strain.[2] However the effect of the polar and steric character of aliphatic substituents β to the C=C–C=O system on the variation of the carbonyl stretching frequency has not been investigated.

In general, a reasonable dependence of $\bar{\nu}_{(C=O)}$ on σ^* was found if the substituents were directly linked to the carbonyl[1,3] and correlations of the type shown in equation (1) have been successfully demonstrated,

$$\bar{\nu}_{(C=O)} = \bar{\nu}^0_{(C=O)} + \rho^*\sigma^* \qquad (1)$$

where $\bar{\nu}^0_{(C=O)}$ is the frequency of the parent member of the series.



SCHEME 1

In this paper we discuss the variation of the carbonyl frequency in three series of nitrogen-substituted (*Z*)- and (*E*)-3-alkylidene-1,3-dihydroindol-2-ones (I)—(III) (Scheme 1).

RESULTS AND DISCUSSION

The above mentioned compounds were prepared from the corresponding alphatic aldehydes and 1,3-dihydroindol-2-one. Base-promoted condensation gave both *Z*- and *E*-isomers which were isolated by chromatography and identified by their n.m.r. spectra (see Table 4 for most significant values).

TABLE 1

Carbonyl stretching frequencies (cm^{-1}) of (*Z*)- and (*E*)- 3-alkylidene-1,3-dihydroindol-2-ones (I)—(III)

					E-(III)		*Z*-(III)	
R²	*E*-(I)	*Z*-(I)	*E*-(II)	*Z*-(II)	Lactam	Acetyl	Lactam	Acetyl
Me	1 701.2	1 797.7	1 714.8	1 711.8	1 743.1	1 706.8	1 739.9	1 705.7
Et	1 700.0	1 697.9	1 712.8	1 710.6	1 740.4	1 706.8	1 737.4	1 705.8
Prⁱ	1 699.3	1 697.9	1 711.6	1 710.0	1 738.6	1 706.6	1 737.1	1 706.0
Et_2CH	1 698.6	1 698.0	1 711.2	1 710.0	1 738.2	1 707.0	1 736.5	1 705.9
Buᵗ	1 698.0	1 698.1	1 709.9	1 709.4	1 736.9	1 707.0	1 740.1	1 705.7

The carbonyl stretching frequencies were measured in $CHCl_3$ solutions (for details see Experimental section) and their values are listed in Table 1.

Whereas both *N*-methyl- (I) and *N*-acetyl- (III) substituted derivatives show a carbonyl absorption independent of concentration, great care has to be taken with the unsubstituted compounds (II). Their carbonyl absorption is largely concentration dependent and a dilution study over the range 0.1—0.0001M showed that only at high dilution (0.0005M) does the position of the band and its shape undergo no further modification. This is due to the presence of both CO and NH groups which cause the formation of intermolecular hydrogen bonds[4] and therefore the values reported were taken at a suitable concentration to avoid these associations.

Examination of simple molecular models shows that the *Z*-configuration, in spite of the five-membered ring

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[1] For a general survey see, A. R. Katritzky and R. D. Topson in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London and New York, 1972, p. 120.

[2] G. Desimoni, V. Di Toro, G. Tacconi, O. Azzolina, and V. Ghislandi, *Gazzetta*, in the press.

[3] C. Pascual and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 1344.

[4] A. H. Beckett, R. W. Daisley, and J. Walker, *Tetrahedron*, 1968, **24**, 6093.

strain,[2,5] involves non-negligible steric interactions between the alkyl group and the oxygen lone pairs.

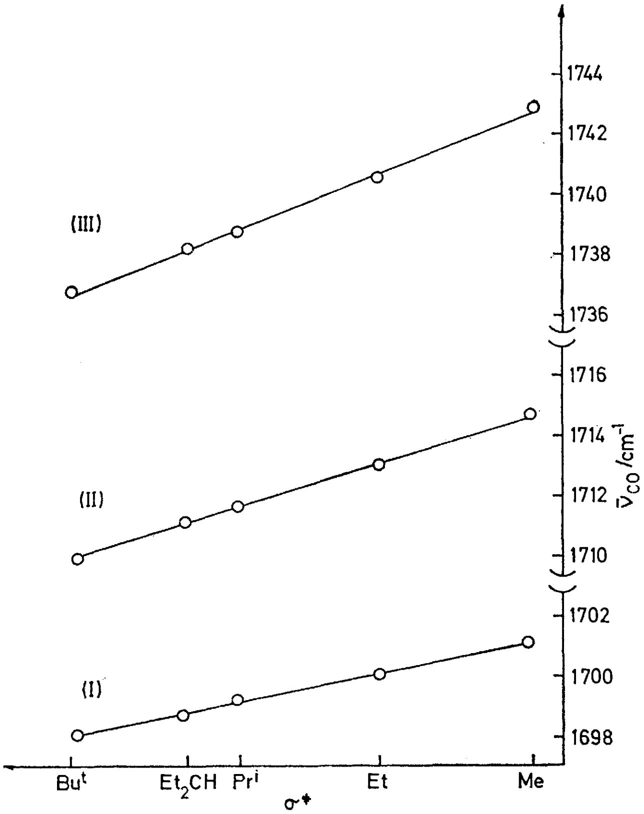
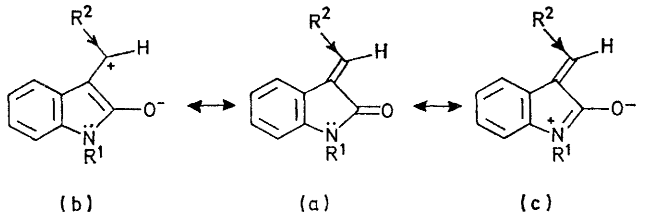


FIGURE 1 Plot of $\tilde{\nu}_{(C=O)}$ against σ* for *E*-(I)—(III)

Therefore we have considered the *E*-series first; $\bar{\nu}_{(C=O)}$ values were plotted against Taft's σ* values[6] and the results are shown in Figure 1.

Good correlations were obtained for all three series [*r* 0.995, 0.996, and 0.992 for (I)—(III) respectively]. This suggests that the variation of the carbonyl stretching frequency is mainly due to the inductive effect of the alkyl group which increases the contribution of the 1,4-dipolar form [(b) in Scheme 2] in proportion to increase in electron-releasing effect of the group.



SCHEME 2

The ρ* values vary and increase in the order (III) > (II) > (I) (20.501, 15.867, and 10.677 respectively). Since a comparable degree of planarity of the C=C–C=O system can be suggested for the three series (even a t-butyl group does not seem to induce appreciable twisting since this value does not deviate from linearity) the variation of ρ* can probably be rationalized in terms of the different degree of participation of the nitrogen lone pair in conjugation with the carbonyl group and depends on the different behaviour of the nitrogen substituents [Scheme 2, (a) and (c)].

The 1,3-dipolar form (c) is stabilized by electron-releasing *N*-alkyl substituents, but its contribution is considerably decreased if the nitrogen lone pair can be delocalized by the *N*-acyl group. Therefore the transmission in the αβ-unsaturated carbonyl system is greatly decreased if the resonance R–$\ddot{N}$–C=O is in competition with C=C–C=O, whereas it is increased when the former is negligible.

The *Z*-series have to be considered somewhat differently. When $\bar{\nu}_{(C=O)}$ values were plotted against σ* (Figure 2) only (I) gave a good linear correlation, but only because this series is almost insensitive to substituent effects (ρ* −1.229; mean value 1 697.9 cm^{-1} with a standard deviation of 0.15).

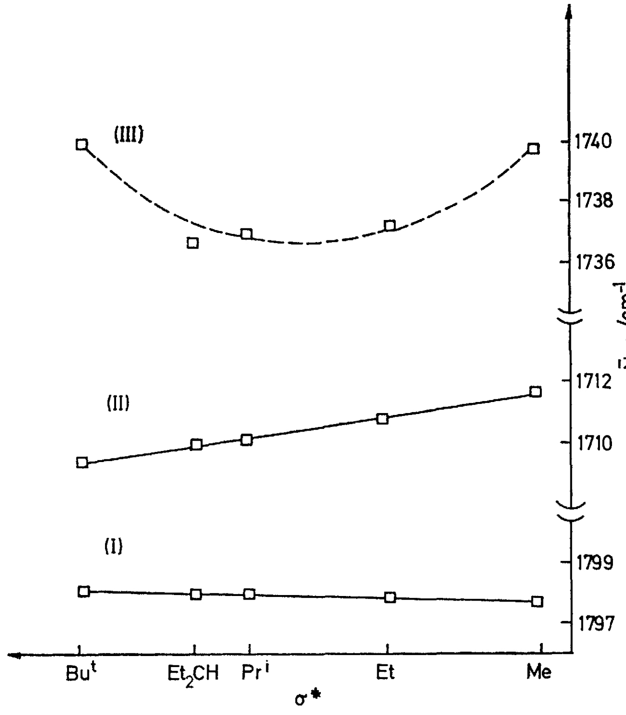


FIGURE 2 Plot of $\tilde{\nu}_{(C=O)}$ against σ* for *Z*-(I)—(III)

The N–H substituted series (II) gave a ρ* value of 7.673 with a correlation coefficient of 0.979, whereas the acetyl derivatives (III) gave a parabola, a shape which can also be detected in (II).

The reason for this behaviour can be rationalized in

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[5] G. Cellerino, G. Desimoni, P. P. Righetti, and G. Tacconi, *Gazzetta*, 1973, **103**, 1247.

[6] R. W. Taft in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, ch. 13.

[7] R. W. Woodard and D. W. Boykin, jun., *Chem. Comm.*, 1970, 628.

terms of competition between steric and electronic effects.[7] If the alkyl group in the β-position is small, the twist of the C=C–C=O system is not significant and inductive effects take over. When a bulky group (Pr^i, Et_2CH, or Bu^t) twists the unsaturated carbonyl because of steric hindrance, the loss of resonance increases $\bar{\nu}_{(C=O)}$ and counterbalances or eventually exceeds the inductive effect. This effect is clear as the contribution of the dipolar form [Scheme 2, (c)] is negligible and therefore lies in the order (I) < (II) < (III).

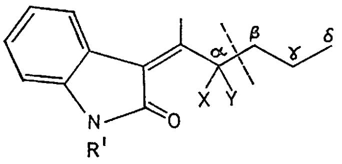

FIGURE 3 Steric interactions in indoles (I)—(III)

A quantitative approach in terms of the separation of polar and steric effects can be performed with a Taft-type equation (2). Unfortunately Taft steric parameters E_s are a function of the Van der Waals radius of the whole alkyl group[8] whereas in the steric interactions mentioned previously only a small part of the alkyl group, the α-region (Figure 3), plays a relevant role. The chain extending outwards from the β-carbon atoms does not interact significantly with the carbonyl oxygen atom.

$$\bar{\nu}_{(C=O)} = \bar{\nu}^0_{(C=O)} + \rho^*\sigma^* + \delta E_s \qquad (2)$$

We have therefore adopted a set of E_s values (E^{α}_s) which corresponds to the E_s value[6] of the simpler group with the same α-part of the alkyl residue (Me = 0.00; Et = −0.07; Pr^i = −0.47; Et_2CH = −0.47; Bu^t = −1.54).*

Figure 4 shows the graphic representation of the least squares and multiple regression treatment of the stretching frequency data of Z-(III) which is given by equation (2): $\bar{\nu}_{(C=O)} = 1\,739.93 + 27.40\sigma^* - 5.37E^{\alpha}_s$ (r 0.995).

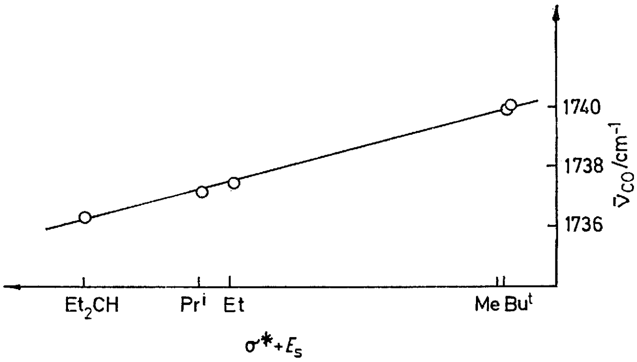

FIGURE 4 Plot of $\bar{\nu}_{(C=O)}$ against the sum of polar (σ^*) and steric (E^{α}_s) parameters for Z-(III)

The data for Z-(II) can also be analysed using the same method and if $\bar{\nu}^0_{(C=O)}$, ρ^*, and δ are respectively 1 711.68, 8.97, and −0.28, the correlation coefficient becomes 0.984.

Acetyl stretching frequencies are nearly constant in both E- and Z-(III): mean values 1 706.8 and 1 705.8, standard deviations 0.17 and 0.13 respectively, the insensitivity being expected because of the lack of conjugation and the distance between the centres involved.

Further evidence of the variation of the carbonyl electron density can be obtained from the chemical shift of the vinyl proton H_v (Table 4). Its variation is a function of (i) deshielding of the dihydroindolone phenyl ring for Z-isomers, which could be considered as a constant independent of the nature of the alkyl group; (ii) anisotropic deshielding of the lactam carbonyl group for E-isomers; (iii) the different shielding of the various alkyl groups both for E- and Z-isomers and the different variation in conjugation induced by them.

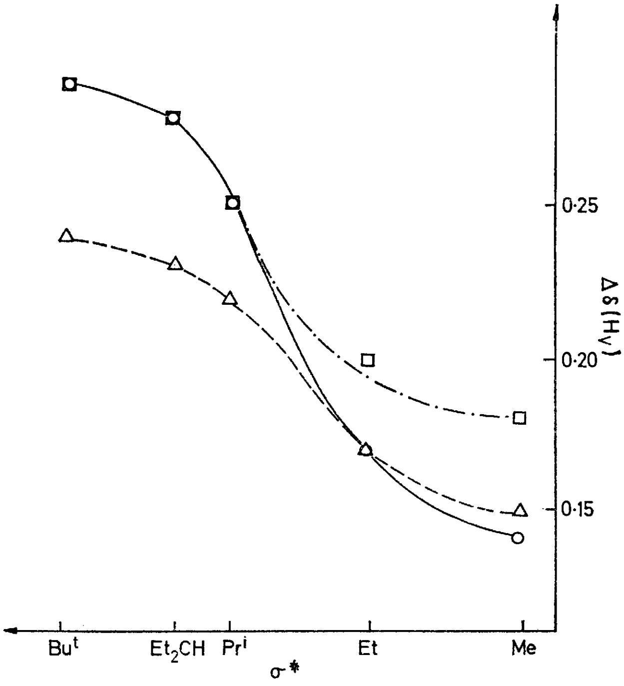

FIGURE 5 Plot of σ^* against E and Z chemical shift difference of the vinylic proton: □ (I); ○ (II); △ (III)

To minimize the third point, the differences $\Delta\delta(H_v) = \delta(H_v^E) - \delta(H_v^Z)$ were plotted *versus* σ^* to show the effect of the second point (Figure 5).

If the alkyl groups have the same shielding effect in the Z- and E-configurations, the $\Delta\delta(H_v)$ variation can be assigned to a change in the anisotropy of the carbonyl group due to the inductive effect of the alkyl group in addition to the different degree of conjugation between

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* The Pr^n, Bu^i, and Bu^n derivatives of E- and Z-(I)—(III) were also prepared but the results are omitted since they were essentially the same as for the Et derivatives. $\bar{\nu}_{(C=O)}$ Values correlate with σ^* and using the E^{α}_s value −0.07, all Z-(III) compounds fit nicely on the line reported in Figure 4. Data are available on request.

[8] M. Charton, *J. Amer. Chem. Soc.*, 1969, **91**, 615.

the *Z*- and *E*-series. The lack of linearity has no special meaning since at the moment we do not know how the inductive effect and the anisotropy are connected.

$\Delta\delta(H_v)$ is greater for (I) than for (III) due to the effect of nitrogen substituents which increase the shielding power of the lactam carbonyl group. Furthermore we cannot exclude that the twist of the C=C–C=O system, induced by bulky substituents in the *Z*-configuration, can modify the shape of the curves in the region concerned, in addition to the effect of the hydrogen-bonded dimers of (II) because of the concentration required in the solutions for n.m.r. spectra.

In conclusion, the inductive effect of alkyl groups in the β-position of the αβ-unsaturated carbonyl system is transmitted to the carbonyl group producing significant variations in the stretching frequency.

TABLE 2

Analytical and physical data for compounds (I)—(II)

Compound	Reaction time (h) [total yield (%)]	Physical aspect (*E* : *Z* ratio)	M.p. (°C) or T_{subl} (°C) [*p*/mmHg]	Elemental analysis (%)
E-(Ia)	6 [63—64]	Soft light yellow needles (83.5)	78—79 [e]	Found: C, 76.1; H, 6.5; N, 8.1
Z-(Ia)		Yellow needles (16.5)	65—67 [f]	Found: C, 76.1; H, 6.55; N, 8.15 Calc. for $C_{11}H_{11}NO$: C, 76.25; H, 6.4; N, 8.1
E-(Ib)	13 [52—53]	Soft yellow needles (71.5)	53—54 [f]	Found: C, 76.75; H, 7.2; N, 7.5
Z-(Ib)		Yellow oil [a] (28.5)	90—95 [0.10]	Found: C, 76.8; H, 7.1; N, 7.5 Calc. for $C_{12}H_{13}NO$: C, 76.95; H, 7.0; N, 7.5
E-(Ic)	8 [53—54]	Soft yellow needles (69)	54—55 [f]	Found: C, 77.7; H, 7.45; N, 6.8
Z-(Ic)		Yellow oil [a] (31)	80—85 [0.10]	Found: C, 77.7; H, 7.6; N, 6.85 Calc. for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 6.95
E-(Id)	20 [77—78]	Yellow oil [a] (70)	90—95 [0.25]	Found: C, 78.25; H, 8.45; N, 6.15
Z-(Id)		Yellow oil [a] (30)	90—95 [0.10]	Found: C, 78.6; H, 8.5; N, 6.2 Calc. for $C_{15}H_{19}NO$: C, 78.5; H, 8.35; N, 6.1
E-(Ie)	24[39—40]	Yellow oil [a] (67.5)	105—110 [0.10]	Found: C, 78.0; H. 7.7; N, 6.65
Z-(Ie)		Yellow crystals (32.5)	58—59 [f]	Found: C, 78.2; H, 8.15; N, 6.6 Calc. for $C_{14}H_{17}NO$: C, 78.1; H, 7.95; N, 6.5
E-(IIa) [b,c,h]	5 [69—70]	Yellow needles (79)	140—142 [g]	
Z-(IIa) [b,c,i]		Soft yellow needles (21)	173—174 [g]	
E-(IIb) [d,j]	10 [68—69]	Yellow platelets (72)	100—101 [f]	
Z-(IIb) [c,k]		Soft yellow needles (28)	151—153 [f]	
E-(IIc)	6 [57—58]	Yellow needles (75)	119—120 [e]	Found: C, 77.0; H, 7.2; N, 7.35
Z-(IIc)		Soft yellow needles (25)	133—135 [e]	Found: C, 77.45; H, 7.11; N, 7.4 Calc. for $C_{12}H_{13}NO$: C, 76.95; H, 7.0; N, 7.5
E-(IId)	20 [64—65]	Pale yellow platelets (70)	135—136 [e]	Found: C, 78.4; H, 8.0; N, 6.7
Z-(IId)		Yellow platelets (30)	138—139 [e]	Found: C, 78.2; H, 7.9; N, 6.6 Calc. for $C_{14}H_{17}NO$: C, 78.1; H, 7.95; N, 6.5
E-(IIe)	24 [50—53]	Yellow platelets (66)	133—134 [e]	Found: C, 77.85; H, 7.6; N, 6.85
Z-(IIe)		Yellow needles (34)	175—176 [e]	Found: C, 77.35; H, 7.6; N, 6.8 Calc. for $C_{13}H_{15}NO$: C, 77.6; H, 7.5; N, 6.96

[a] Stable for a few days at 0°. [b] Described with the correct configuration.[10] [c] Described with undetermined configuration [11—14] [d] Erroneously described as *Z*-isomer.[10] [e] From ligroin. [f] From light petroleum. [g] From benzene. [h] Lit. m.p. 139—141;[10] 140;[11]; 141—144;[12] 143.5—145;[13] 142°.[14] [i] Lit. m.p. 177—178;[10] 165;[11] 164—169°.[13] [j] Lit. m.p. 97—98°.[10] [k] Lit m.p. 143°.[11]

A rationalization of the experimental results is more difficult for alkyl than for *para*-substituted aryl groups since electronic effects in the former case can be balanced and sometimes exceeded by steric factors, particularly in the *Z*-configuration. Nevertheless, at least for alkylidenedihydroindolones, careful combination of both effects seems to explain the observed data.

EXPERIMENTAL

All m.p.s are uncorrected. N.m.r. spectra were obtained by Dr A. Gamba Invernizzi.

Indolones (I) *and* (II). *General Method.*—A mixture of 1-methyl-1,3-dihydroindol-2-one [9] or 1,3-dihydroindol-2-one (0.01M), the appropriate aldehyde (5 ml), and a dry 10% solution of Me_3N in ether (2.5 ml) was heated on an oil-bath at 100° in a Paar bomb. After cooling, the solution was evaporated at 100° under vacuum and the oily residue was treated several times with EtOH and evaporated. Finally

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[9] M. S. Kisteneva, *Zhur. obshchei Khim.*, 1956, **26**, 1169.

[10] G. Tacconi and S. Pietra, *Il Farmaco Ed. Sci.*, 1963, **18**, 409.

[11] L. Horner, *Annalen*, 1941, **548**, 141.

[12] H. Kondo, T. Nozoye, and M. Tobita, *Ann. Reports Itsum Lab.*, 1952, **3**, 70 (*Chem. Abs.*, 1953, **47**, 7488c).

[13] H. Kondo, T. Nozoye, and M. Tobita, *Ann. Reports Itsum Lab.*, 1950, **1**, 32 (*Chem. Abs.*, 1953, **47**, 3857f).

[14] E. Wenkert, B. S. Bernstein, and J. H. Udelhofen, *J. Amer. Chem. Soc.*, 1958, **80**, 4899.

the yellow oil or solid residue was chromatographed (column length 80 cm, diam. 4.5 cm; kieselgel 0.06—0.02; cyclohexane–ethyl acetate 7 : 3 as eluant). Pure *Z*- and *E*-isomers were obtained as the first and second fractions respectively. Anhydrous sodium sulphate (3.5 g) was added to the initial mixture when starting from acetaldehyde. After dilution of the cooled suspension with diethyl ether, the inorganic residue was filtered off and the mother liquors were treated as described above.

Reaction times, yields, and physical characteristics of the isomers are reported in Table 2.

I.r. Frequencies.—The i.r. frequencies were determined using a Perkin-Elmer 421 spectrophotometer operating in the expanded scale (×5) at scan rates of 10 cm^{-1} min^{-1}. Calibration was performed using bands at 1 801.6 and 1 601.4 cm^{-1} of polystyrene film. The spectra were taken on freshly prepared solutions [0.08M for (I) and (III); 0.0005M for (II)] of the indoles in spectral grade pure chloroform at room temperature in NaCl cells of path length 0.10 [(I) and (III)] or 1.00 mm [(II)]. The values reported in Table 1 are the average of 3—5 different scans and the maximum deviation observed was in the range ±0.3 cm^{-1}. The results were reproducible for different samples. The carbonyl bands of *Z*-(IIIc—e) are atypically complex because a shoulder is present. The band shape used to determine $\bar{\nu}_{(C=O)}$ was obtained by superimposition of the spectrum of *Z*-(IIIa) and plotting the resulting curve graphically. Statistical treatment of data was performed on a Hewlett–Packard 9805 A computer table.

TABLE 3

Analytical and physical data for compounds (III)

Compound	Physical aspect (*E* : *Z* ratio)	M.p. (°C)	Elemental analysis (%)
E-(IIIa)	Soft light pink needles (60)	100—101 [a]	Found: C, 71.5; H, 5.6; N, 6.85
Z-(IIIa)	White crystals (40)	119—120.5° [b]	Found: C, 71.5; H, 5.7; N, 6.8 Calc for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 6.95
E-(IIIb)	Soft white needles (70)	87—88 [a]	Found: C, 72.35; H, 5.8; N, 6.3
Z-(IIIb)	White needles (30)	65—67	Found: C, 72.5; H, 5.9; N, 6.4 Calc for $C_{13}H_{13}NO_2$: C, 72.55; H, 6.1; N, 6.5
E-(IIIc)	White crystals (70)	103—104 [a]	Found: C, 73.2; H, 6.4; N, 6.05
Z-(IIIc)	Soft white needles (30)	81—82 [a]	Found: C, 73.3; H, 6.4; N, 5.85 Calc for $C_{14}H_{15}NO_2$: C, 73.5; H, 6.6; N, 6.1
E-(IIId)	White platelets (90)	55—56 [a]	Found C, 74.5; H, 7.3; N, 5.3
Z-(IIId)	White crystals (10)	54—55 [a]	Found: C, 74.4; H, 7.4; N, 5.25 Calc for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.45; N, 5.4
E-(IIIe)	White crystals (70)	103—104 [a]	Found: C, 73.8; H, 7.1; N, 5.5
Z-(IIIe)	Light pink crystals (30)	112—113 [a]	Found: C, 73.9; H, 7.0; N, 5.6 Calc for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.0; N, 5.75

[a] From light petroleum. [b] From ligroin.

TABLE 4

N.m.r. data (δ)

Compound	H_v	ΔH_v	H_α [a]	Compound	H_v	ΔH_v	H_α [a]	Compound	H_v	ΔH_v	H_α [a]
E-(Ia)	7.06 (q)	0.17	2.22 (d)	*E*-(IIa)	7.08 (q)	0.13	2.22 (d)	*E*-(IIIa)	7.14 (q)	0.14	2.26 (d)
Z-(Ia)	6.89 (q)		2.43 (d)	*Z*-(IIa)	6.95 (q)		2.44 (d)	*Z*-(IIIa)	7.00 (q)		2.44 (d)
E-(Ib)	7.00 (t)	0.19	2.66 (qt)	*E*-(IIb)	7.01 (t)	0.16	2.68 (qt)	*E*-(IIIb)	7.06 (t)	0.16	2.70 (m)
Z-(Ib)	6.81 (t)		3.01 (qt)	*Z*-(IIb)	6.85 (t)		2.03 (qt)	*Z*-(IIIb)	6.90 (t)		2.97 (m)
E-(Ic)	6.88 (d)	0.24	3.26 (m)	*E*-(IIc)	6.90 (d)	0.24	3.25 (m)	*E*-(IIIc)	6.94 (d)	0.21	3.25 (m)
Z-(Ic)	6.64 (d)		4.17 (m)	*Z*-(IIc)	6.66 (d)		4.14 (m)	*Z*-(IIIc)	6.73 (d)		4.00 (m)
E-(Id)	6.85 (d)	0.27	2.92 (m)	*E*(IId)	6.86 (d)	0.27	2.90 (m)	*E*-(IIId)	6.90 (d)	0.22	3.05 (m)
Z-(Id)	6.58 (d)		3.87 (m)	*Z*-(IId)	6.59 (d)		3.85 (m)	*Z*-(IIId)	6.68 (d)		3.55 (m)
E-(Ie)	7.21 (s)	0.28		*E*-(IIe)	7.20 (s)	0.28		*E*-(IIIe)	7.24 (s)	0.23	
Z-(Ie)	6.93 (s)			*Z*-(IIe)	6.92 (s)			*Z*-(IIIe)	7.01 (s)		

[a] See Figure 3.

Indolones (III).—A solution of (II) (4 mmol) in Ac_2O (16 ml) was heated under reflux for *ca.* 2 h. The solution was evaporated to dryness and the residue chromatographed (cyclohexane–ethyl acetate 9 : 1 as eluant) as reported above for (I) and (II). Pure *Z*- and *E*-isomers (Table 3) were obtained and the total yield was almost quantitative.

N.m.r. Spectra.—The n.m.r. spectra were obtained on a Perkin-Elmer R 12A spectrometer operating at 60 MHz. The samples (0.2 mmol) of (I)—(III) were dissolved in $CDCl_3$ (0.4 ml) containing tetramethylsilane as internal standard. The spectra, with internal lock, were taken in three runs. Decoupling experiments support the reported attributions. The main values and parameters are reported in Table 4.

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