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HETERODIENE SYNTHESES—V[1]

1,2- VERSUS 1,4-CYCLOADDITION REACTIONS OF ENAMINES TO N-SUBSTITUTED 3-OXINDOLIDENEACETOPHENONES[2]

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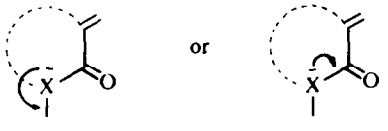
Abstract—The reaction of some enamines with N-substituted 3-oxindolideneacetophenones has been investigated. When the oxindole N-substituent is an acyl group, 1,4-cycloaddition occurs leading to 2,3-dihydropyrano[2,3-*b*]indole derivatives· when the N-substituent is an alkyl group, 1,2-cycloaddition takes place and spirocyclobutanoxindole derivatives are formed. Some intermediate cases are also presented. A possible rationalisation of the electronic effect N-substituent on the reaction pathway is proposed.

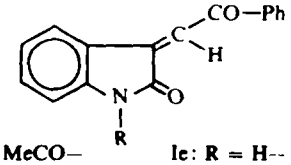
IN PREVIOUS papers we have shown that the α,β-unsaturated carbonyl system of N-acyl-3-benzaloxindoles reacts with vinyl ethers[3] and enamines[4] undergoing 1,4-cycloaddition.

This reaction has been successfully extended to a large series of other heterocyclic derivatives[3,5] and the only products obtained have always implied a 1,4-cycloaddition.

Since in all heterocyclic compounds tested the heteroatom in α-position to the carbonyl group carries one or more lone pairs, we have investigated the role played by this lone pair in the cycloaddition. In theory the lone pair delocalization, due to different groups being located *e.g.* on the nitrogen atom, could perturb the α,β-unsaturated system in opposite directions:



In the present paper the reaction of enamines with 3-oxindolideneacetophenones, N-substituted either with electron-attracting (acyl) or electron-repelling (alkyl) groups or with intermediate (H, benzyl or substituted benzyls) groups, is reported.



Ia: R = MeCO—		**Ie**: R = H—	
b: = PhCO—		f: = $PhCH_2$—	
c: = Me—		g: = p.MeO.C_6H_4.CH_2—	
d: = Et—		h: = p.NO_2.C_6H_4.CH_2—	

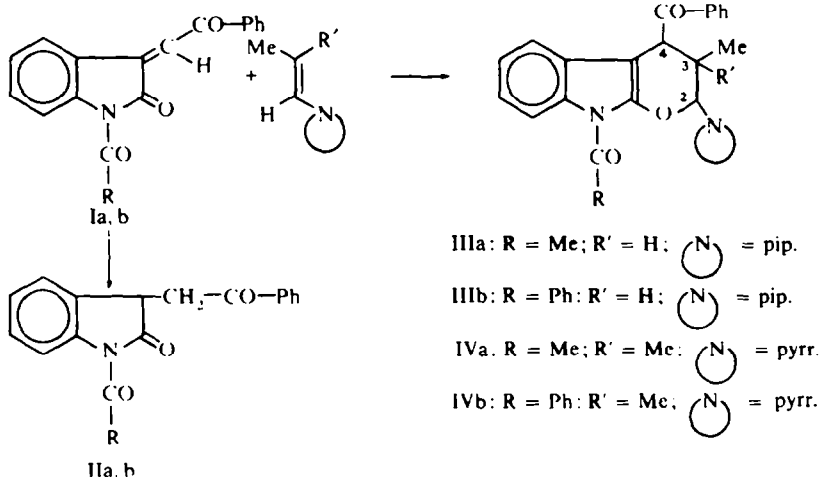
Moreover oxindolidene derivatives (I) possess a second α,β-unsaturated carbonyl system in the side chain, which can be regarded as a new reacting center for the cycloaddition. *A priori*, in addition to the different possible cycloaddition reactions, a Michael addition involving both unsaturated carbonyl systems should also be considered, all the more since such a reaction has been invoked for analogous derivatives.[6] We have therefore tested two different enamines, 1-piperidino-1-propene (E_1) whose structure would allow a Michael type addition, and 1-pyrrolidino-1-isobutene (E_2), for which this reaction is obviously impossible.

The stereochemistry of the initial oxindolideneacetophenones is probably *trans*, since all their NMR spectra show a sharp singlet between 7·82 and 7·98 δ, which can be assigned to the vinyl proton. These values are fully consistent with previously described *trans*-oxindolidene derivatives[7] and the small paramagnetic shift with respect to *trans*-3-oxindolideneacetones[8] is probably due to the deshielding effect of the benzene ring.

1,4-*Cycloaddition*

All N-acylsubstituted oxindole derivatives reacted with both enamines E_1 and E_2 and colourless but quite unstable adducts were obtained in high yields. The results are reported in Scheme I.

SCHEME I



In addition to the adducts IIIa, b and IVa, b, we prepared starting from the reactants Ia, b the hydrogenated derivatives, since a comparison of the IR spectra of all these compounds would allow us to infer the nature of the addition reaction, as Table 1 shows.

From the data reported above it can be seen that all adducts have: (i) no lactam C=O band; (ii) no exocyclic C=C band; (iii) a shift of the α,β-unsaturated C=O band, attributed to relief of conjugation.

Therefore, both the double bond and the lactam carbonyl group must have participated in the reaction, and hence a 1,4-cycloaddition is strongly suggested.

TABLE 1

Compd	ν C=C exocyclic	ν C=C dihydropyr.	ν C=O lactam	ν C=O acyl	ν C=O ketone
Ia	1628 m	—	1745 s	1720 s	1660 s
IIa	absent	—	1743 s	1720 s	1680 s
IIIa	absent	1630 s	absent	1690 s	1678 s
IVa	absent	1631 s	absent	1710 s	1673 s
Ib	1625 m	—	1730 s	1692 s	1665 s
IIb	absent	—	1730 s	1701 s	1684 s
IIIb	absent	1638 s	absent	1685 s	1680 s
IVb	absent	1641 s	absent	1685 s	1680 s

Furthermore all adducts show a strong band in the region characteristic of C=C double bonds in dihydropyran rings condensed with oxindoles.[4]

The NMR spectra† of adducts IIIa, b were, due to their instability, registered at -20^{c} and they exclude the presence of isomers; the main values are reported in Table 2. All other protons of the base and of the aromatic rings showed consistent chemical shift values.

TABLE 2

Compd	Methyl dihydropyr.	H_2	H_4	R	Note
IIIa	1·10 d	4·47 d	4·37 d	methyl	H_3 is
	J 6·5	$J_{2,3}$ 10·0	$J_{3,4}$ 9·0	2·66 s	overlapped by
IIIb	0·97 d	4·57 d	4·34 d	phenyl	H_a of the
	J 6·5	$J_{2,3}$ 10·0	$J_{3,4}$ 9·0	(arom)	piperidine

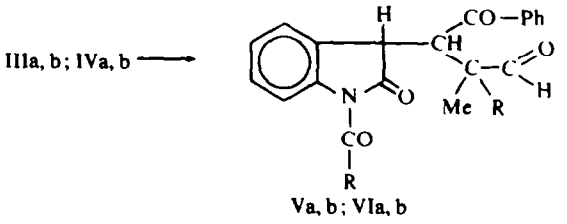
The chemical shift of the dihydropyran methyl group is consistent with its being located on a six-membered ring.[9] The small paramagnetic shift of H_2 in IIIb, compared with IIIa, is probably due to the deshielding effect of the benzene ring of the N-acyl group.

The large values for the coupling constants of the dihydropyran protons, compared with similarly condensed dihydropyran derivatives,[1] clearly indicates that in all cases a *trans* coupling occurs, the relationship between the hydrogens being largely axial–axial. Whereas this is to be expected between H_2 and H_3, owing to the stereochemistry of the starting enamine,[10] a similar coupling between H_3 and H_4 is very interesting, since it confirms the strong stereospecificity of the reaction. A similar stereospecificity has been shown to control the cycloadditions between *cis*- and *trans*-propenyl propyl ethers and arylidenepyrazolones or isoxazolones.[11]

The proposed orientation of the cycloaddition was confirmed by hydrolytic cleavage of all adducts under mild conditions (Scheme II).

† Chem shifts are reported in ppm on the δ scale, coupling constants in cps; $CDCl_3$ was the solvent and TMS the internal standard.

SCHEME II



Va, b; VIa, b

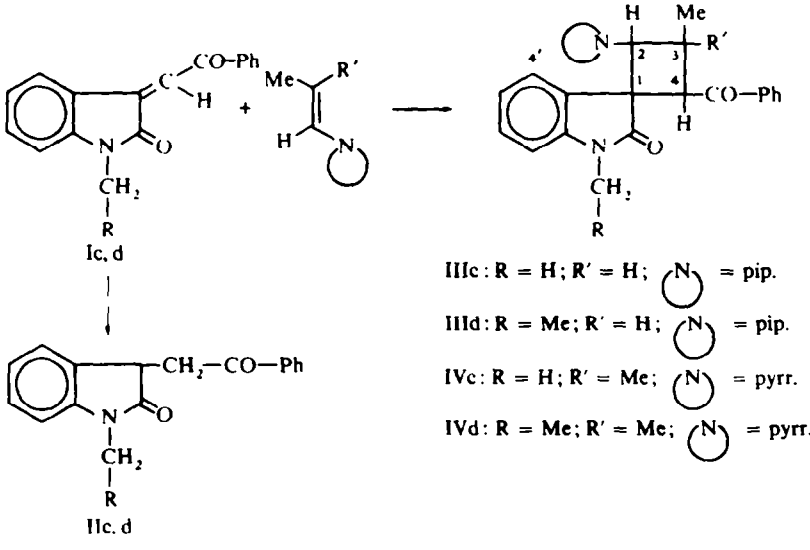
Open-chain 3-substituted oxindole derivatives (Va, b; VIa, b) were obtained and their structures, shown by their NMR spectra, which are reported in the experimental section (Tables 11–12). allow us to exclude a 1,4-cycloaddition reaction on the unsaturated carbonyl system of the side chain.

Some of the above mentioned aldehyde derivatives existed as a mixture of two configurational isomers, the presence of two or three chiral carbon atoms in their structures fully explaining this occurrence.

1,2-*Cycloaddition*

N-Methyl and N-ethyl-3-oxindolideneacetophenones (Ic, d) reacted with the enamines E_1 and E_2 in an entirely different manner (Scheme III).

SCHEME III



The IR spectra of the adducts, reported in Table 3 together with those of the starting compounds and their hydrogenated derivatives (IIc, d), again allow us to deduce what type of reaction has taken place. An inspection of the data clearly shows that the labile point on the substrate now is only the exocyclic double bond.

All adducts lack the band due to stretching of the exocyclic double bond and show a corresponding shift in the band due to the α,β-unsaturated ketone system

TABLE 3

Compd	ν C=C exocyclic	ν C=O lactam	ν C=O ketone
Ic	1625 m	1700 s	1660 s
IIc	absent	1700 s	1685 s
IIIc	absent	1700 s	1680 s
IVc	absent	1705 s	1680 s
Id	1620 m	1700 s	1658 s
IId	absent	1705 s	1670 s
IIId	absent	1692 s	1685 s
IVd	absent	1695 s	1683 s

deriving from relief of conjugation; moreover no trace appears of the band assigned to the dihydropyran double bond.

Starting from E_2 there is no valid alternative to a 1,2-cycloaddition scheme; starting from E_1 the presence of a hydrogen atom in the β-position does not allow us *a priori* to exclude a Michael type reaction. However, this latter possibility is very unlikely, since in the IR spectra of the adducts the band due to the enamine double bond no longer appears. The NMR spectra, registered at −20° (Table 4), allow us to neglect this last remote possibility. The relevant details are the chemical shift of the methyl group, whose value is consistent with its location on a four membered ring,[12] and its coupling constant, which excludes the allylic coupling required in a Michael type adduct.

TABLE 4

Compd	Methyl (cyclobutane)	H_4	H_4·	N | R	Aromatics
IIIc	1·38 d *J* 5·5	3·79 d *J* 9·0	6·39 m	methyl 3·05 s	6·7–7·5 m
IIId	1·35 d *J* 6·0	3·83 d *J* 9·0	6·48 m	ethyl 1·07 t 3·74 q *J* 5·5	6·9–7·1 m

The low field doublet is assigned to the proton α- to the carbonyl group (H_4), the proton α- to the base (H_2) is partly overlapped by the N-Me signal and by the equatorial protons of the base. The signal near the aromatic region can be reasonably attributed to the proton in position 4′ on the oxindole ring, which is particularly shielded by the cyclobutane substituents.

Decoupling experiments were performed on IIIc (Fig 1), in order to discover the chemical shift of the third cyclobutane proton (H_3); the only position where both the signals of the cyclobutane methyl group and of H_4 become singlets is 3·08 δ. The proximity of the H_3 and H_2 signals can probably be explained in terms of the

combined deshielding effect of the carbonyl and the piperidine nitrogen, if we assume for these adducts a stereochemistry analogous to that in the previously described dihydropyran derivatives, *i.e.* with the methyl group *trans* both to the benzoyl and to the base group.

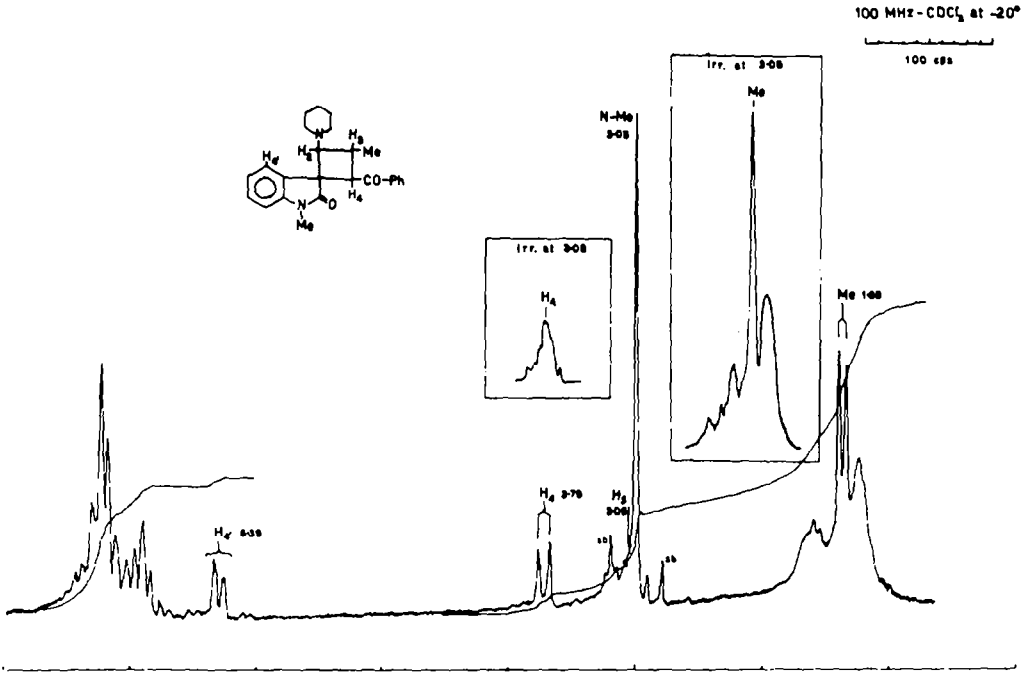
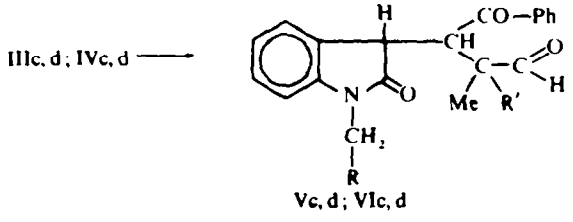


FIG 1. NMR spectrum of spiro [(2-piperidyl-3-methyl-4-benzoyl)cyclobutane-1,3'-(1'-methyl) oxindole] (IIIc) and its spin decoupling spectra

SCHEME IV



Hydrolytic cleavage of the adducts under mild conditions (Scheme IV), yielded the aldehyde derivatives Vc, d and VIc, d, whose structures, demonstrated by NMR spectroscopy (Tables 11–12 in the experimental section), again confirm the direction of the cycloaddition. A fully decoupled spectrum of Vc is shown in Fig 2.

Intermediate Cases

Since the oxindole N-substituents seemed to play a leading role in the electronic control of the reaction, we next investigated substrates with substituents having

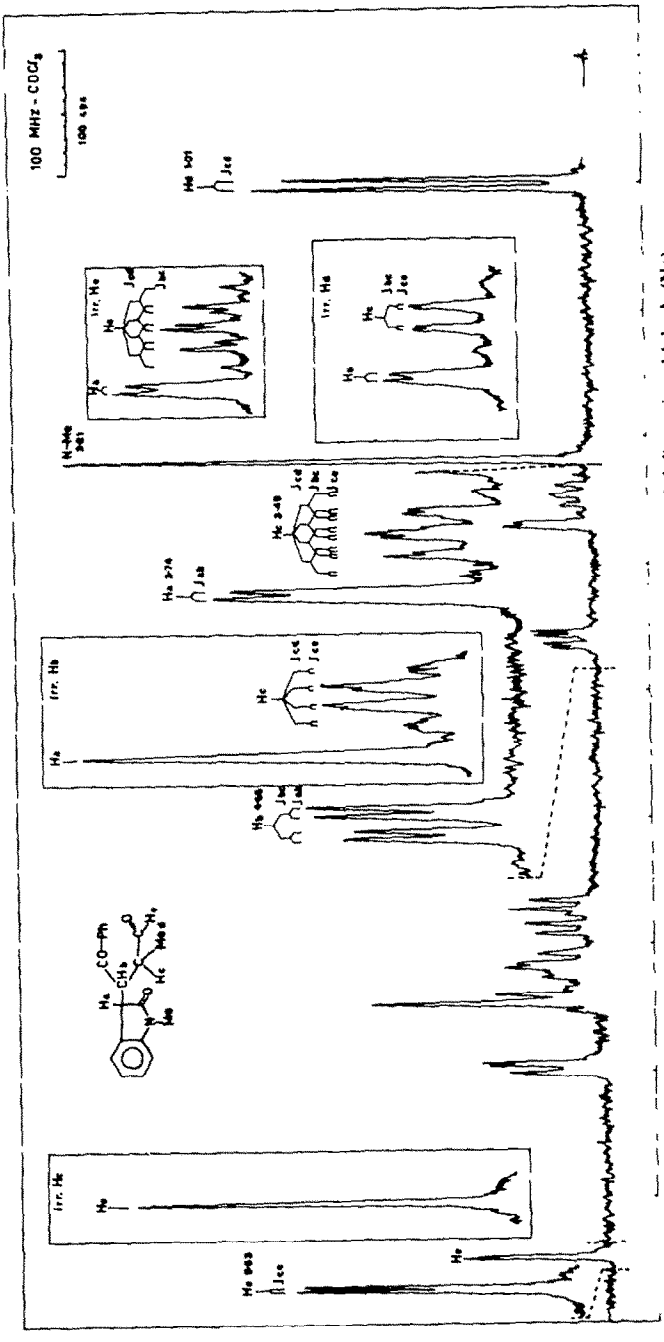
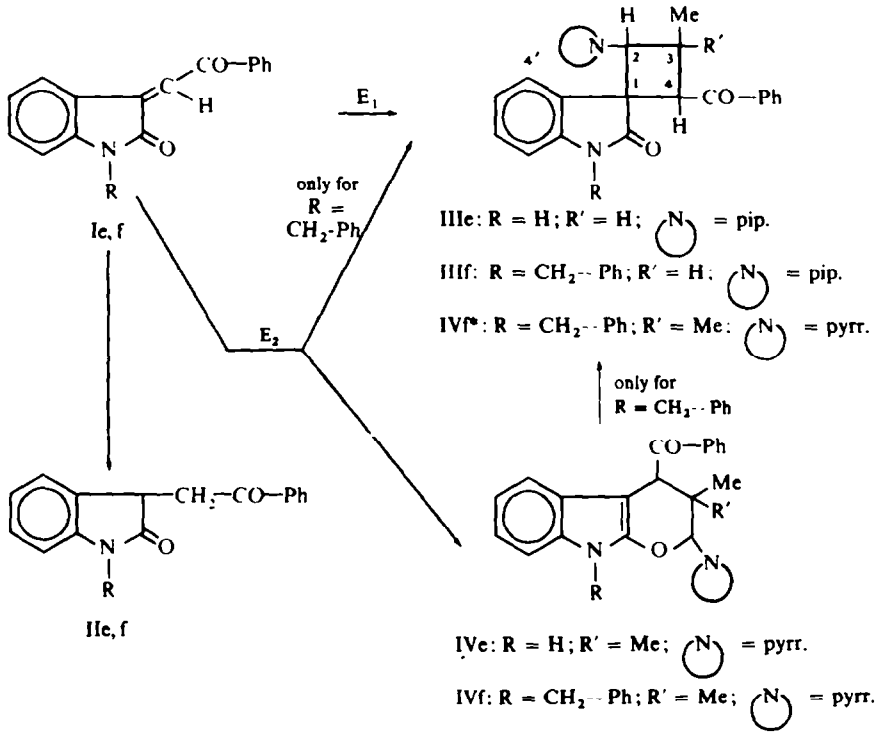


FIG 2. NMR spectrum of α-methyl-β-benzoyl-β-(1-methyl-3-oxindolyl)propionaldehyde (Vc) and its spin decoupling spectra

intermediate effects to those in the previously considered cases. N-Unsubstituted (Ie) and N-benzyl-3-oxindolideneacetophenone (If) reacted with the enamines E_1 and E_2 following the Scheme V.

SCHEME V



A comparison between the IR spectra (Table 5) of the adducts (IIIe, f; IVe, f, f*) and those of the starting material (Ie, f) and of IIe, f gave conclusive evidence of the nature of the reactions.

TABLE 5

Compd	ν C=C exocyclic	ν C=C dihydropyr	ν C=O lactam	ν C=O ketone
Ie	1620 m	--	1710 s	1655 s
IIe	absent	--	1705 s	1685 s
IIIe	absent	absent	1705 s	1679 s
IVe	absent	1625 s	absent	1680 s
If	1620 m	--	1710 s	1659 s
IIf	absent	--	1710 s	1688 s
IIIf	absent	absent	1708 s	1675 s
IVf	absent	1630 s	absent	1672 s
IVf*	absent	absent	1710 s	1670 s

When the oxindole is unsubstituted (Ie) the reaction with the enamine E_1 gives a 1,2-cycloaddition product (IIIe), whereas the reaction with the enamine E_2 yielded a 1,4-cycloaddition product (IVe).

When the oxindole is N-benzyl substituted (If), the enamine E_1 still gives a cyclobutane adduct (IIIf), while the enamine E_2 gives random results. In the first experiments the only reaction product was IVf, whose spectrum lacks the lactam C=O and the exocyclic double bond, indicating a 1,4-cycloaddition. However, further experiments afforded, besides the first adduct, a second compound (IVf*), which has an IR spectrum fully consistent with a cyclobutane structure, as Fig 3 clearly shows.

The dihydropyran adduct IVf is not stable and, even if stored at $-18°$ in a dark dry place, is slowly converted into the cyclobutane isomer IVf*.

In an attempt to rationalize the results, we changed the molar ratios of the reactants,

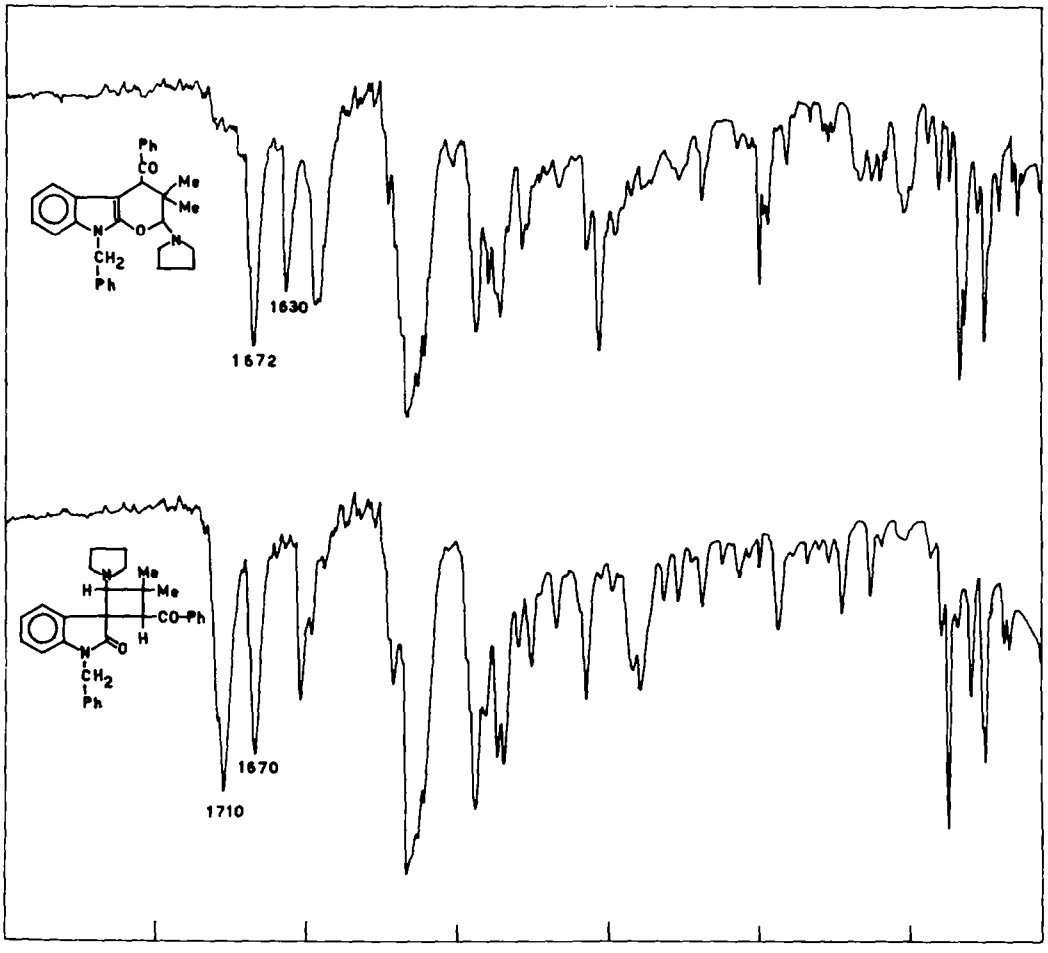
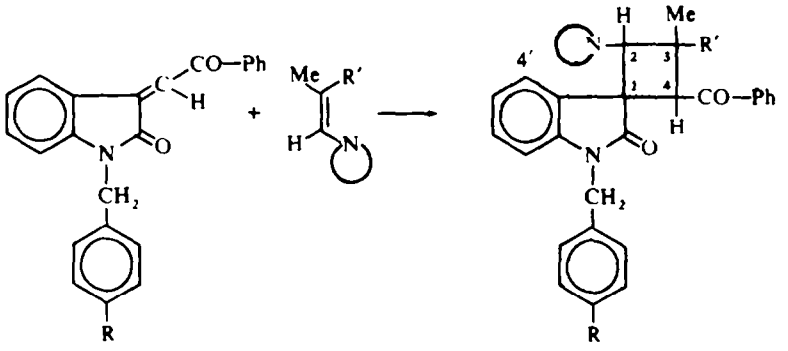


FIG 3. IR spectra (nujol mulls) of 2-(1-pyrrolidinyl)-3,3-dimethyl-4-benzoyl-9-benzyl-2,3-dihydropyrano[2,3-b]indole (IVf) (above) and of spiro [(2-pyrrolidinyl-3,3-dimethyl-4-benzoyl)cyclobutane-1,3'-(1'-benzyl)oxindole] (IVf*) (below)

the reaction temperature and the degree of purity of E_2. Moreover we studied the effect of catalytic amounts of free base on the reaction; but every attempt was unsuccessful and most frequently IVf* was the only reaction product.

In order to study the effect induced by small electronic factors on the two reaction types, we have examined the reactions between N-*p*-methoxybenzyl- (Ig) or N-*p*-nitrobenzyl-3-oxindolideneacetophenone (Ih) and the enamines E_1 and E_2; the results, summarized in Scheme VI, are interpreted by IR spectroscopy. Ih and E_2 gave no isolable material.

SCHEME VI



IIIg: R = OMe; R′ = H; ⟨N⟩ = pip.

IIIh: R = NO_2; R′ = H; ⟨N⟩ = pip.

IVg: R = OMe; R′ = Me; ⟨N⟩ = pyrr.

TABLE 6

Compd	ν C=C exocyclic	ν C=O lactam	ν C=O ketone
Ig	1620 m	1708 s	1660 s
IIIg	absent	1704 s	1675 s
IVg	absent	1705 s	1671 s
Ih	1625 m	1708 s	1662 s
IIIh	absent	1712 s	1672 s

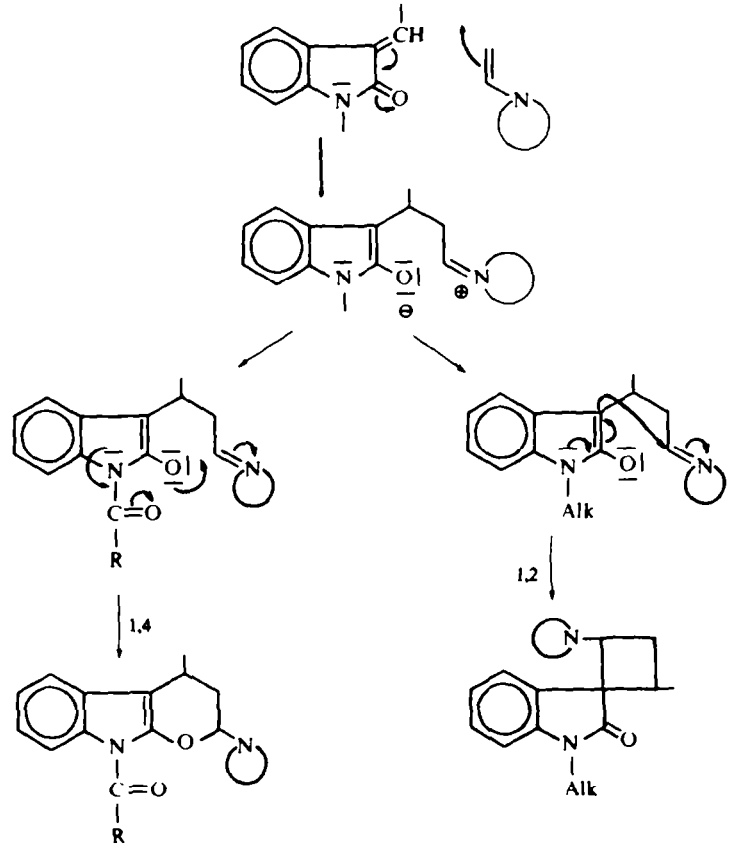
The IR spectra, whose essential data are reported in Table 6, clearly support a 1,2-cycloaddition scheme in all cases, and further evidence arises from an inspection of the NMR spectra, reported in Table 7. IIIe was not measured, owing to its very low solubility, while the main values of IVf* are also reported. As we have previously shown, the reported data demonstrate the presence of a cyclobutane ring, and the methyl couplings in IIIf, g, h again exclude a Michael type addition.

Mild hydrolysis cleaved the adducts IIIe, f, g, h; IVe, f, f*, g and the NMR spectra of the corresponding aldehyde derivatives (Tables 11, 12, 13 and 14 in the experimental section) support the proposed structures.

TABLE 7

Compd	Methyl (cyclobutane)	H_4	$H_{4'}$	N—CH_2—R		Aromatics
				CH_2	R	
IIIf	1·37 d *J* 5·5	3·92 d *J* 9·0	6·33 m	δ_A 4·92 δ_B 4·71 J_{AB} − 16·0	phenyl (arom)	6·8–7·6 m
IIIg	1·36 d *J* 5·5	3·87 d *J* 9·0	6·35 m	δ_A 4·89 δ_B 4·52 J_{AB} − 15·5	*p*-OMe-phenyl 3·75 s	6·7–7·6 m
IIIh	1·41 d *J* 5·5	4·05 d *J* 9·0	6·25 m	5·00 s	*p*-NO_2-phenyl (arom)	6·9–8·2 m
IVf[a]	1·51 s 1·68 s	3·89 s	6·72 m	5·02 s	phenyl (arom)	7·0–7·9 m

SCHEME VII



CONCLUSIONS

From the above facts it is reasonable to conclude that the influence of the N-substituents in 3-oxindolideneacetophenones must be regarded as the sole determinant of the mode of cycloaddition. Their influence may possibly be rationalized as follows: nucleophilic attack of the enamine on the cationic end of the α,β-unsaturated carbonyl system could give rise to a "zwitterionic" intermediate[13] (Scheme VII).

When the nitrogen lone pair is preferentially delocalized on the acyl group, it does not perturb the succeeding ring closure if it follows a 1,4-cycloaddition scheme; however, when the same lone pair is free and enhanced by the inductive effect of the alkyl group, the 3-position of the oxindole becomes more activated and the ring closure occurs by a 1,2-cycloaddition.

When the activation energies for the 1,2- and 1,4-cycloaddition are not comparable, the reaction follows the most favourable reaction coordinate. When the electronic effects modify the energy level of the zwitterion or the activation energies so that these become comparable, a border region is reached, where unknown, but nevertheless very small effects can decide the fate of the actual cycloaddition.

Two facts support these assumptions. First, the spontaneous interconversion, even under very mild conditions, of dihydropyran into cyclobutane derivatives, which can reasonably involve a "zwitterion" intermediate, and secondly the easy modification of the adducts at room temperature, to which we will refer elsewhere.

We believe that such a high sensibility to small electronic factors is noticeable and further work is in progress to provide evidence for the connection between electronic factors and the mode of cycloaddition.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra (nujol mulls) run on a Perkin–Elmer 257 spectrophotometer; NMR spectra, unless otherwise stated, run on a Varian A-60 spectrometer; microanalyses by Dr. Lucia Maggi Dacrema.

1-Substituted isatins

The following isatins, not previously reported, were prepared:

1-p-methoxybenzylisatin. Obtained from isatin and *p*-methoxybenzyl bromide in accordance with the method described for the preparation of 1-benzylisatin.[7] Orange platelets (58%), m.p. 171–172° (EtOH). (Found: C, 72·18; H, 5·00; N, 5·24. Calc for $C_{16}H_{13}NO_3$: C, 71·90; H, 4·90; N, 5·24%).

1-p-nitrobenzylisatin. From isatin and *p*-nitrobenzyl bromide by the above method.[7] Red orange crystals (53%), m.p. 188–189° (AcOH). (Found: C, 63·77; H, 3·74; N, 10·12. Calc for $C_{15}H_{10}N_2O_4$: C, 63·83; H, 3·57; N, 9·93%).

1-Substituted-3-oxindolideneacetophenones (I)

1-acetyl-3-oxindolideneacetophenone (Ia). Prepared by a reported method.[14] NMR: vinylic proton at 7·82 δ (s).

1-benzoyl-3-oxindolideneacetophenone (Ib). To a cooled and stirred soln of 3-oxindolideneacetophenone[15] (12·4 g) in pyridine (190 ml) benzoyl chloride (62 ml) was added dropwise. Cooling and stirring was continued for 1 h, then, after standing overnight at 0°, 0·7 N H_2SO_4 was cautiously added to the cooled, stirred mixture down to pH 3. Ib separated as a yellow ppt (14·45 g, 83%), m.p. 170–171° (EtOH-soft yellow needles). (Found: C, 77·89; H, 4·27; N, 3·99. Calc for $C_{23}H_{15}NO_3$: C, 78·17; H, 4·28; N, 3·96%). NMR: vinylic proton at 7·82 δ (s).

3-oxindolideneacetophenone (Ie). Prepared by a reported method.[15] NMR: vinylic proton at 7·89 δ (s).

1-methyl-3-oxindolideneacetophenone (Ic). Prepared by a reported method.[16] NMR: vinylic proton at

7·89 δ (s). Following this method, from the appropriate isatins, the derivatives reported below were obtained:

TABLE 8

Compd	Physical aspect (yield %)	m.p. (solvent)	Elementary analysis	NMR vynilic proton
Id	red crystals (98)	129–131° (EtOH)	found: C, 77·95; H, 5·64; N, 5·04 for $C_{18}H_{15}NO_2$ calc: C, 77·96; H, 5·45; N, 5·05%	7·89 δ
If	red crystals (93)	128–129° (EtOH)	found: C, 81·39; H, 5·39; N, 4·19 for $C_{23}H_{17}NO_2$ calc: C, 81·39; H, 5·05; N, 4·13%	7·95 δ
Ig	orange needles (85)	141–142° (EtOH)	found: C, 77·59; H, 5·38; N, 4·04 for $C_{23}H_{19}NO_3$ calc: C, 77·29; H, 5·36; N, 3·92%	7·94 δ
Ih	orange soft needles (92)	168–169° (EtOH)	found: C, 71·91; H, 4·26; N, 7·59 for $C_{23}H_{16}N_2O_4$ calc: C, 71·87; H, 4·20; N, 7·29%	7·98 δ

1-*Substituted*-3-*oxindolylacetophenones* (II)

1-*methyl*-3-*oxindolylacetophenone* (IIc). Prepared by a reported method.[17]

3-*oxindolylacetophenone* (IIe). Prepared by a reported method.[15] The following previously unreported 3-oxindolylacetophenones were prepared by hydrogenating at NTP the corresponding 3-oxindolideneacetophenones with CPd 10% (Baker–Enghelhard) catalyst.

TABLE 9

Compd	Hydrog solvent	Physical aspect (yield %)	m.p. (solvent)	Elementary analysis
IIa	EtOH	pale yellow needles (50)	121–122° (EtOH)	found: C, 73·92; H, 5·08; N, 4·79 for $C_{18}H_{15}NO_3$ calc: C, 73·70; H, 5·15; N, 4·78%
IIb	AcOH	soft white needles (80)	142–143° (EtOH)	found: C, 77·93; H, 4·83; N, 3·78 for $C_{23}H_{17}NO_3$ calc: C, 77·73; H, 4·82; N, 3·94%
IId	AcOH	colourless crystals (86)	225–226° (EtOH)	found: C, 77·21; H, 5·91; N, 5·00 for $C_{18}H_{17}NO_2$ calc: C, 77·39; H, 6·13; N, 5·01%
IIf	EtOH	colourless crystals (73)	166–167° (EtOH)	found: C, 80·65; H, 5·67; N, 4·17 for $C_{23}H_{19}NO_2$ calc: C, 80·91; H, 5·61; N, 4·10%

Reactions of I *with enamines*†

2-(1-*piperidyl*)-3-*methyl*-4-*benzoyl*-9-*acetyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IIIa). To a cooled and stirred suspension of Ia (0·87 g, 0·3 mmole) in light petroleum (10·0 ml), 1-piperidino-1-propene (E_1) (0·75 g, 0·6 mmole) was added. The yellow colour slowly disappeared and after 2 h stirring at room temp, the pale pink coloured ppt was filtered off and washed with a large amount of cold light petroleum. IIIa (1·23 g; 99%) was obtained, m.p. 100–102°. (Found: C, 74·84; H, 6·53; N, 6·44. Calc for $C_{26}H_{28}N_2O_3$: C, 74·97; H, 6·78; N, 6·73%).

† All adducts described here are only stable under vacuum at low temp; correct values for the elementary analyses were obtained from crude samples dried for 2 h at room temp, 0·1 mm pressure.

2-(1-*pyrrolidinyl*)-3,3-*dimethyl*-4-*benzoyl*-9-*acetyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IVa). 1-Pyrrolidino-1-isobutene (E_2) (1·87 g, 1·5 mmole) and powdered Ia (0·87 g, 0·3 mmole) were mixed with stirring. After a few mins the cream coloured mass was ground with cold light petroleum and IVa was filtered off and washed with a large amount of light petroleum. Small light-cream coloured crystals (1·05–1·17 g; 84–94%) m.p. 74–75°. (Found: C, 74·79; H, 6·78; N, 6·70. Calc for $C_{26}H_{28}N_2O_3$: C, 74·97; H, 6·78; N, 6·73%).

2-(1-*piperidyl*)-3-*methyl*-4,9-*dibenzoyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IIIb). From Ib (0·3 mmole) and E_1 (0·6 mmole) in light petroleum, as previously described for IIIa, IIIb was obtained (1·35 g; 95%) as light yellow solid, m.p. 93–95°. (Found: C, 77·89; H, 6·31; N, 5·80. Calc for $C_{31}H_{30}N_2O_3$: C, 77·80; H, 6·32; N, 5·85%).

2-(1-*pyrrolidinyl*)-3,3-*dimethyl*-4,9-*dibenzoyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IVb). From Ib (0·3 mmole) and E_2 (1·5 mmole), as previously described for IVa, IVb was obtained (1·35 g; 94%) as light cream coloured crystals product m.p. 90–92°. (Found: C, 77·83; H, 6·55; N, 6·11. Calc for $C_{31}H_{30}N_2O_3$: C, 77·80; H, 6·32; N, 5·85%).

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*methyl*)*oxindole*] (IIIc). From a suspension of Ic (0·3 mmole) in light petroleum (10·0 ml) and E_1 (0·6 mmole), IIIc was obtained, in accordance with the method previously described for IIIa, as white crystalline ppt (0·95–1·05 g; 80–91%) m.p. 97–98°. (Found: C, 77·11; H, 7·22; N, 6·95. Calc for $C_{25}H_{28}N_2O_2$: C, 77·29; H, 7·27; N, 7·21%).

Spiro [(2-*pyrrolidinyl*-3,3-*dimethyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*methyl*)*oxindole*] (IVc). Following the method described for IVa, from Ic (0·3 mmole) and E_2 (1·5 mmole), IVc was prepared as white solid (1·05 g; 91%) m.p. 92–93°. (Found: C, 77·30; H, 7·35; N, 7·20. Calc for $C_{25}H_{28}N_2O_2$: C, 77·29; H, 7·27; N, 7·21%).

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*ethyl*)*oxindole*] (IIId). In accordance with the above method for IIIa, from a suspension of Id (0·3 mmole) in light petroleum (10·0 ml) but using 1·5 mmole of E_1, IIId was obtained as white solid (0·96 g; 81%) m.p. 105–106°. (Found: C, 77·34; H, 7·77; N, 6·86. Calc for $C_{26}H_{30}N_2O_2$: C, 77·58; H, 7·51; N, 6·96%).

Spiro [(2-*pyrrolidinyl*-3,3-*dimethyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*ethyl*)*oxindole*] (IVd). As described for IVa, from Id (0·3 mmole) and E_2 (1·5 mmole), IVd was prepared as pale pink solid (1·08 g; 90%) m.p. 113–115°. (Found: C, 77·37; H, 7·50; N, 6·80. Calc for $C_{26}H_{30}N_2O_2$: C, 77·58; H, 7·51; N, 6·96%).

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-*oxindole*] (IIIe). To a suspension of Ie (0·3 mmole) in benzene (3·0 ml), E_1 (1·2 mmole) was added. In about 1 h all the starting material had dissolved and, after evaporation of the benzene at room temp, the residue was ground with cold light petroleum. IIIe (0·87 g; 80%) was obtained as small light pink crystals m.p. 95–97°. (Found: C, 76·85; H, 7·07; N, 7·35. Calc for $C_{24}H_{26}N_2O_2$: C, 76·97; H, 7·00; N, 7·48%).

2-(1-*pyrrolidinyl*)-3,3-*dimethyl*-4-*benzoyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IVe). As described for IVa, from Ie (0·3 mmole) and E_2 (1·5 mmole), IVe was obtained after standing for a long time at 0°, in quantitative yield (1·02 g) as small white crystals m.p. 75–77°. (Found: C, 76·75; H, 6·80; N, 7·74. Calc for $C_{24}H_{26}N_2O_2$: C, 76·97; H, 7·00; N, 7·48%).

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*benzyl*)*oxindole*] (IIIf). Following the method described for IIIa but from If (0·3 mmole) and E_1 (1·5 mmole) in light petroleum, IIIf was obtained (1·2 g; 87%) as a white solid m.p. 111–113°. (Found: C, 80·50; H, 6·91; N, 6·12. Calc for $C_{31}H_{32}N_2O_2$: C, 80·14; H, 6·94; N, 6·03%).

Reaction of If *with* E_2. (a) 2-(1-*pyrrolidinyl*)-3,3-*dimethyl*-4-*benzoyl*-9-*benzyl*-2,3-*dihydropyrano* [2.3-b] *indole* (IVf). Powdered If (0·34 g; 0·1 mmole) and E_2 (0·2 or 0·3 or 0·5 mmole) were mixed at 0° and after respectively 1 week, 3 days, 1 night, the red colour disappeared and a light green crystalline solid separated in near quantitative yield. If the reaction was performed at room temperature, it was completed in a shorter period and with almost the same yield. IVf is obtained as light green crystals m.p. 90–91°. (Found: C, 79·60; H, 7·16; N, 5·80. Calc for $C_{31}H_{32}N_2O_2$: C, 80·14; H, 6·94; N, 6·03%).

(b) *Spiro* [(2-*pyrrolidinyl*-3,3-*dimethyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-*benzyl*)*oxindole*] (IVf*). From the same reactants in the same ratios and at the same temp, IVf* was obtained as light cream coloured crystals in nearly quantitative yield m.p. 89–91°. (Found: C, 79·80; H, 7·06; N, 6·27. Calc for $C_{31}H_{32}N_2O_2$: C, 80·14; H, 6·94; N, 6·03%).

(c) Sometimes at 0°, light green crystals of IVf and cream prisms of IVf* are formed together. When mechanically separated, they give IR spectra superimposable on those from the products respectively obtained from (a) and (b).

(d) A sample of IVf (0·2 g), stored at −18°, fully isomerized after about 1 month into IVf* as shown from the IR spectrum.

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-p-*methoxybenzyl*)*oxindole*] (IIIg). As pre-

viously described for IIIa, but from Ig (0·3 mmole) and E_1 (1·2 mmole) in light petroleum at 0°, IIIg was obtained (1·2 g; 82%) as small light cream crystals m.p. 98–101°. (Found: C, 77·36; H, 7·15; N, 5·75. Calc for $C_{31}H_{34}N_2O_3$: C, 77·15; H, 7·10; N, 5·81%).

Spiro [(2-*pyrrolidinyl*-3,3-*dimethyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-p-*methoxybenzyl*)*oxindole*] (IV g). As for IVa, but from Ig (0·3 mmole) and E_2 (1·5 mmole), IVg was obtained (1·2 g; 82%) as light cream crystals m.p. 98–100 with softening at about 76°. (Found: C, 77·47; H, 7·09; N, 5·80. Calc for $C_{31}H_{34}N_2O_3$: C, 77·15; H, 7·10; N, 5·81%).

Spiro [(2-*piperidyl*-3-*methyl*-4-*benzoyl*)*cyclobutane*-1,3'-(1'-p-*nitrobenzyl*)*oxindole*] (IIIh). As described for IIIa, but from Ih (0·3 mmole) and E_1 (1·2 mmole) in benzene (1·5 ml), and after dilution of the reaction mixture and grinding of the ppt with cold light petroleum, IIIh was obtained as white solid (1·35 g; 90%) m.p. 112–114°. (Found: C, 73·60; H, 6·13; N, 8·20. Calc for $C_{31}H_{31}N_3O_4$: C, 73·06; H, 6·13; N, 8·25%).

Hydrolytic cleavage of III *and* IV

α-*methyl*-β-*benzoyl*-β-(1-*acetyl*-3-*oxindolyl*)*propionaldehyde* (Va). IIIa (1·23 g; 0·3 mmole) was added to a cooled and stirred mixture of AcOH (6 ml) and H_2O (1 ml). Stirring and cooling was continued for

TABLE 10

Compd	Hydrolysis conditions: AcOH (ml)	H_2O (ml)	Reaction time	Yield %	m.p. (solvent)	Elementary analysis	
Vb	18	3	2½ h	84†	148–149° (EtOH)	for $C_{26}H_{21}NO_4$	found: C, 75·87; H, 4·92; N, 3·47 calc: C, 75·89; H, 5·14; N, 3·40%
Vc	5	5	1 h	95	114–115° (EtOH)	for $C_{20}H_{19}NO_3$	found: C, 74·52; H, 5·98; N, 4·60 calc: C, 74·74; H, 5·96; N, 4·36%
Vd	6	6	1 h	84	122–124° (EtOH)	for $C_{21}H_{21}NO_3$	found: C, 75·46; H, 6·46; N, 4·18 calc: C, 75·20; H, 6·31; N, 4·18%
Ve	6	6	30 min	90	159–161° (EtOH)	for $C_{19}H_{17}NO_3$	found: C, 74·15; H, 5·69; N, 4·61 calc: C, 74·25; H, 5·58; N, 4·56%
Vf	9	9	3 h	76	143·5–144·5° (PhH/dIPE 1:3)	for $C_{26}H_{23}NO_3$	found: C, 78·81; H, 6·00; N, 3·41 calc: C, 78·57; H, 5·83; N, 3·52%
Vg	21	21	6 h	89	105–107° (PhH/dIPE 1:3)	for $C_{27}H_{25}NO_4$	found: C, 75·98; H, 6·00; N, 3·41 calc: C, 75·86; H, 5·90; N, 3·28%
Vh	13	13	24 h	95	135–136° (PhH/dIPE 1:3)	for $C_{26}H_{22}N_2O_5$	found: C, 70·70; H, 4·84; N, 6·30 calc: C, 70·58; H, 5·01; N, 6·33%
VIa	6	12	5 min	51†	104–105° (EtOH)	for $C_{22}H_{21}NO_4$	found: C, 72·41; H, 5·84; N, 3·88 calc: C, 72·71; H, 5·82; N, 3·85%
VIb	13	13	15 min	91†	153–154° (EtOH)	for $C_{27}H_{23}NO_4$	found: C, 76·51; H, 5·45; N, 3·25 calc: C, 76·22; H, 5·45; N, 3·29%
VIc	9	9	1 h	95	150–151° (EtOH)	for $C_{21}H_{21}NO_3$	found: C, 75·08; H, 6·38; N, 4·28 calc: C, 75·20; H, 6·31; N, 4·18%
VId	12	24	1 h	99	164–166° (PhH/dIPE 1:2)	for $C_{22}H_{23}NO_3$	found: C, 75·84; H, 6·65; N, 4·16 calc: C, 75·62; H, 6·63; N, 4·01%
VIe	6	6	15 min	71	178–179° (EtOH)	for $C_{20}H_{19}NO_3$	found: C, 74·47; H, 6·03; N, 4·42 calc: C, 74·74; H, 5·96; N, 4·36%
VIf	9	9	20 h	88‡	114–116° (PhH/dIPE 1:3)	for $C_{27}H_{25}NO_3$	found: C, 78·57; H, 6·11; N, 3·61 calc: C, 78·81; H, 6·12; N, 3·40%
VIg	12	12	20 h	93	128–130° (PhH/dIPE 1:2)	for $C_{28}H_{27}NO_4$	found: C, 76·08; H, 6·15; N, 3·39 calc: C, 76·17; H, 6·16; N, 3·17%

† Together with byproducts referred to elsewhere

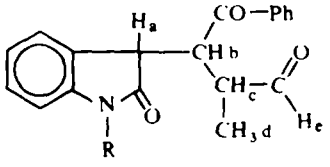
‡ Same conditions and yields from IVf and IVf*

40 mins, then the white ppt was filtered and washed with a large amount of water. Va (0·9 g; 87%) was obtained as small white crystals m.p. 134–136°. Small samples of Va could be crystallized from EtOH (m.p. 136–137°), taking care to avoid prolonged boiling. (Found: C, 72·44; H, 5·55; N, 4·21. Calc for $C_{21}H_{19}NO_4$: C, 72·19; H, 5·48; N, 4·01%).

Following the previously described method, from 0·3 mmole of adduct, the following aldehyde derivs (V and VI) were obtained (Table 10).

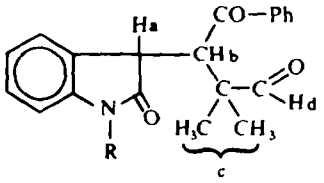
The main values for the NMR spectra of V and VI are summarized in Tables 11–14.

TABLE 11



Compd	H_a	H_b	H_c	H_d	H_e	R	Aromatics
Va	3·88 d J_{ab} 3·2	4·64 q J_{ab} 3·2 J_{bc} 10·0	3·61 o J_{bc} 10·0 J_{cd} 7·2	1·04 d J_{cd} 7·2	9·57 s	acetyl 2·75 s	6·75–8·38 m
Vb	3·99 d J_{ab} 3·5	4·69 q J_{ab} 3·5 J_{bc} 10·0	3·75 o J_{bc} 10·0 J_{cd} 7·2	1·03 d J_{cd} 7·2	9·61 s	benzoyl (arom)	6·80–8·40 m
Vc	3·74 d J_{ab} 3·5	4·65 q J_{ab} 3·5 J_{bc} 10·0	3·49 m J_{bc} 10·0 J_{cd} 7·1 J_{ce} 1·5	1·01 d J_{cd} 7·1	9·53 d J_{ce} 1·5	methyl 3·21 s	6·61–8·25 m
Vd	3·73 d J_{ab} 3·0	4·63 q J_{ab} 3·0 J_{bc} 9·5	3·50 m J_{bc} 9·5 J_{cd} 7·0 J_{ce} 1·2	1·10 d J_{cd} 7·0	9·57 d J_{ce} 1·2	ethyl 1·30 t 3·78 q J 7·0	6·66–8·16 m
Ve	3·80 d J_{ab} 3·0	4·68 q J_{ab} 3·0 J_{bc} 9·5	3·56 m J_{bc} 9·5 J_{cd} 7·2 J_{ce} 1·0	1·05 d J_{cd} 7·2	9·60 d J_{ce} 1·0	hydrog 8·83 broad signal	6·65–8·30 m

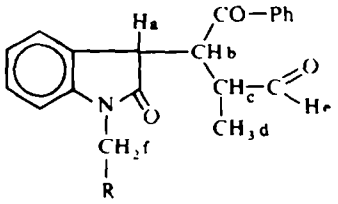
TABLE 12



Compd	H_a	H_b	H_c	H_d	R	Aromatics	Ratio of isomers
Isom A	4·10 d J_{ab} 6·0	4·51 d J_{ab} 6·0	1·15 s 1·55 s	9·65 s	acetyl 2·58 s	6·83–8·15 m	66%
VIa							
Isom B	3·92 d J_{ab} 2·2	4·51 d J_{ab} 2·2	1·26 s 1·29 s	9·67 s			34%
Isom A	4·01 d J_{ab} 3·0	4·62 d J_{ab} 3·0	1·25 s 1·26 s	9·67 s	benzoyl (arom)	6·83–8·15 m	70%
VIb							
Isom B	4·21 d J_{ab} 6·0	4·61 d J_{ab} 6·0	1·17 s 1·47 s				30%
Isom A	3·84 d J_{ab} 4·5	4·47 d J_{ab} 4·5	1·17 s 1·29 s	9·80 s	methyl 2·96 s	6·35–8·06 m	70%
VIc							
Isom B	3·73 d J_{ab} 2·5	4·55 d J_{ab} 2·5	1·50 s	9·75 s	methyl 3·05 s		30%
Isom A	3·88 d J_{ab} 5·0	4·48 d J_{ab} 5·0	1·52 s 1·27 s	9·82 s	ethyl 1·08 t 3·57 q J 7·0		79%
VId						6·45–8·15 m	
Isom B	†	4·57 d J_{ab} 2·5	1·17 s	9·77 s	ethyl 1·11 t (†) J 7·0		21%
Isom A	3·80 d J_{ab} 2·5	4·59 d J_{ab} 2·5	1·17 s 1·19 s	9·73 s	hydrog 9·05	6·51–8·05 m	49%
VIe							
Isom B	3·89 d J_{ab} 5·0	4·50 d J_{ab} 5·0	1·25 s 1·49 s		broad signal		51%

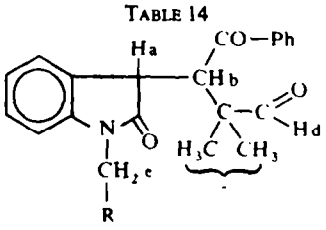
† Overlapped by protons of the other isomer

TABLE 13



Compd	H_a	H_b	H_c	H_d	H_e	H_f	R	Aromatics
Vf	3·90 d J_{ab} 3·4	4·73 q J_{ab} 3·4 J_{bc} 9·4	3·75 o J_{bc} 9·4 J_{cd} 7·7	1·03 d J_{cd} 7·7	9·65 s	4·95 s	phenyl (arom)	6·55–8·20 m
Vg	3·84 d J_{ab} 3·5	4·68 q J_{ab} 3·5 J_{bc} 9·5	3·59 m J_{bc} 9·5 J_{cd} 7·0 J_{ce} 1·0	1·01 d J_{cd} 7·0	9·61 d J_{ce} 1·0	4·86 s	*p*-OMe-phenyl 3·74 s	6·56–8·16 m
Vh	3·95 d J_{ab} 3·5	4·77 q J_{ab} 3·5 J_{bc} 9·7	3·85 m J_{bc} 9·7 J_{cd} 7·5 J_{ce} 0·75	1·07 d J_{cd} 7·5	9·73 d J_{ce} 0·75	δ_A 5·18 δ_B 4·95 J_{AB} −16·0	*p*-NO_2-phenyl (arom)	6·45–8·41 m

TABLE 14



	H_a	H_b	H_c	H_d	H_e	R	Aromatics	Ratio of isomers
Isom A	4·07 d J_{ab} 5·15	4·60 d J_{ab} 5·15	1·30 s 1·60 s	9·75 s	δ_A 4·89 δ_B 4·68 J_{AB} −15·4	phenyl (arom)	6·50–8·00 m	50%
VIf								
Isom B	3·93 d J_{ab} 2·25	4·71 d J_{ab} 2·25	1·22 s 1·24 s	9·71 s	δ_A 4·87 δ_B 4·72 J_{AB} −14·25			50%
Isom A	4·01 d J_{ab} 5·5	4·54 d J_{ab} 5·5	1·23 s 1·56 s	9·80 s	δ_A 4·71 δ_B 4·56 J_{AB} −15·5	*p*-OMe-phenyl	6·36–8·00 m	79%
VIg								
Isom B	†	†	1·15 s 1·17 s	9·70 s	†	3·75 s		21%

† Overlapped by protons of the other isomer

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