Tetrahedron Vol 31, pp 1179 to 1189 Pergamon Press 1975 Printed in Great Britain

HETERODIENE SYNTHESES—XIV[1]

THE REACTION OF 3-OXINDOLIDENEACETOPHENONES WITH ETHYL VINYLETHER

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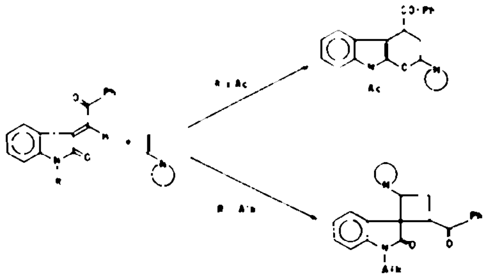
(*Received in the UK* 14 *October* 1974; *Accepted for publication* 24 *November* 1974)

Abstract—Ethyl vinylether reacts with 3-oxindolideneacetophenones. In addition to some 2,3-dihydropyran[2,3-b]indoles, obtained by 1,4-cycloaddition, previously unknown 3-(3-oxindolyl)dihydrofurans whose origin may involve a dipolar intermediate were isolated. Rationalization of the mechanism is proposed and the approach in terms of frontier orbitals is discussed.

In previous papers of this series we have considered the reaction of α,β-unsaturated carbonyl compounds of the heterocyclic series with nucleophilic olefins. Vinyl ethers gave condensed dihydropyran derivatives by 1,4-cycloaddition only,[2] whereas enamines gave a variety of reactions, 1,4- or 1,2-cycloaddition[3] and sometimes a Michael reaction[4] depending on the enamine and the substrate.

3-Oxindolideneacetophenones underwent 1,2- or 1,4-cycloaddition with aldo-enamines depending on the oxindolic nitrogen residue[5] (Scheme 1).



Scheme 1.

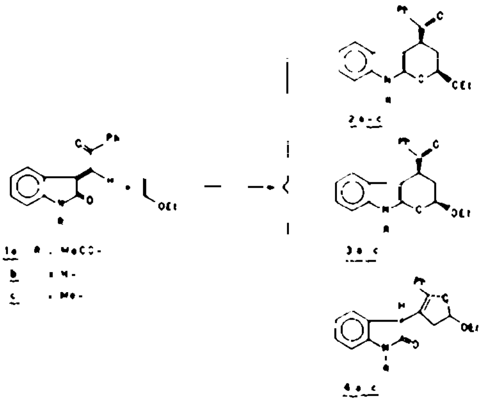
If R is an electron-attracting substituent the delocalization of the nitrogen lone pair addition leads to dihydropyran derivatives. However an electron-donating substituent favours delocalization of the same lone pair onto the α,β-unsaturated carbonyl system and cyclization leads to spiro-cyclobutane derivatives. Some borderline cases occur with R = H or CH_2Ph, and in these cases the choice between 1,4- or 1,2-cycloaddition depends on the nature of the enamine.

Using this behaviour as model, we have approached the reaction with ethyl vinyl ether of three different *N*-substituted 3-oxindolideneacetophenones **1 a-c**, with *E* configuration.[3,5]

The course of the reaction is not dependent on the nature of the nitrogen substituent because in general three products are formed from acetyl-, methyl- and unsubstituted-oxindolidene derivatives. The yields (Table 1) are different, but one isomer is always predominant and the minor one is sometimes absent.

The structure of the adducts (Scheme 2) were investigated by IR (Table 2).

The above-reported IR data clearly suggest that the adducts **2** and **3** have a similar dihydropyran structure, possibly regioisomers or diastereoisomers, since both C=C and lactam C=O groups are involved in the reaction. The third isomer **4 a-c** differs both from a dihydropyran and a spirocyclobutane structure, as the lactam C=O is not involved and the site of reaction involves both C=C and keto C=O groups.



Scheme 2.

Therefore **4 a-c** can have an oxindole-dihydrofuran structure involving the above groups. Their NMR spectra (Table 8, Experimental) are fully in accordance with the structures, even though they show the crude adducts to be diastereoisomeric mixtures. A single isomer was usually isolated on crystallization but the configuration of each single isomer is not very important due to the possibility of racemization of the oxindolic chiral center.

In order to distinguish between a regioisomeric or diastereoisomeric structure for **2 a-c** and **3 a,c** and to show that **4 a-c** has the reported structure we have investigated the chemical behaviour of the adduct (Scheme 3).

On mild acid hydrolysis, all adducts **2**, **3** and **4** from the same nitrogen-substituted isomers gave the same open-chain polycarbonyl compounds **5 a-c**. These aldehydes are amorphous materials whose NMR can be clearly interpreted only for N-acetylsubstituted **5 a**. **5 b** and **5 c** were therefore converted into the acetals **6 b,c** whose NMR (see Experimental) are consistent with the proposed structure. Furthermore they were also obtained directly by nucleophilic ring opening of **2**, **3** and **4 b,c** with ethanol.

The γ-dicarbonylic structure of **5 b,c** was further supported since 3-(3-oxindolyl)furans **7 b,c** were obtained in accordance with the Paal-Knorr reaction. The same

Table 1.

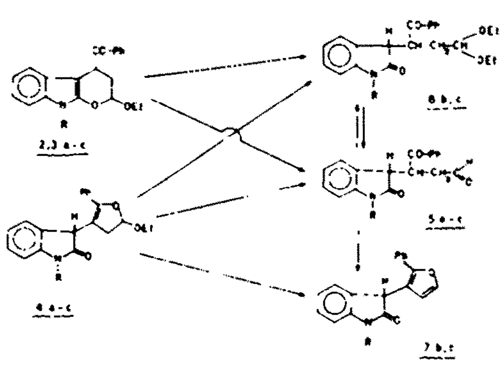
1	Adducts total yield %	3%	3%	4%[a]
a	89	76	8	5
b	~75	35–60	---	12–18
c	75	50	9	16

[a]Diastereomeric mixtures.

Table 2. IR spectra of starting products and adducts

Compd	ν C=C exocyclic	ν C=C dihydropyr.	ν C=O lactam	ν C=O ketone	ν C=O acetyl
1a	1633 s	------	1750 s	1665 s	1725 s
2a	absent	1649 s	absent	1690 s	1700 s
3a	absent	1648 s	absent	1682 s	1708 s
4a	absent	absent	1765 s	absent	1712 s
1b	1620 s	------	1710 s	1655 s	------
2b	absent	1630 s	absent	1675 s	------
4b	absent	absent	1710 s	absent	------
1c	1625 s	------	1700 s	1660 s	------
2c	absent	1635 s	absent	1690 s	------
3c	absent	1635 s	absent	1688 s	------
4c*	absent	absent	1718 s	absent	------

*Film



Scheme 3.

compounds were obtained via thermic elimination from the oxindolic-dihydrofuran adducts 4 b,c.

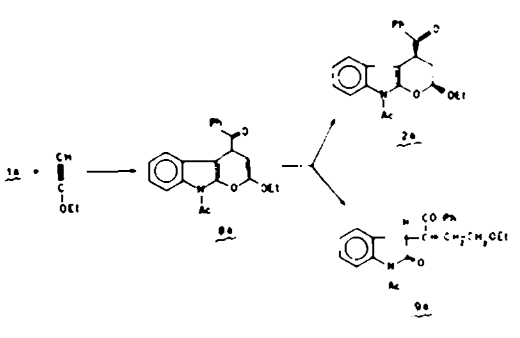
The sequence of reactions supports the proposed structures and therefore 2 and 3 must be diastereoisomers.

The best way to distinguish between cis and trans configurations of a condensed dihydropyran is by NMR; however, all the reported adducts (see Table 7—Experimental) give rise to an A_2MX spectrum in $CDCl_3$. Good ABMX spectra were obtained in acetone in a few cases only.

Although analogies in chemical shift values and the spectrum of 2 b in acetone suggest a cis configuration for 2 a-c and a trans configuration for 3 a,c, stricter attribution was ensured by a chemical correlation.

The reaction of 1 a with ethoxyethyne gave a good yield of the condensed pyran-indole 8 a, as well as coloured materials which we shall consider elsewhere.[6] It is well known that the catalytic reduction of these adducts is highly stereoselective[2b,7] due to the preferred adsorption of the molecule on the catalyst from the less hindered side. Therefore when 8 a was reduced with H_2/Pd–C (Scheme 4), a high yield of the cis isomer 2 a was obtained in addition to some open-chain product 9 a.

The possibilities that equilibration occurs during the reaction, and that 4 is a primary reaction product have

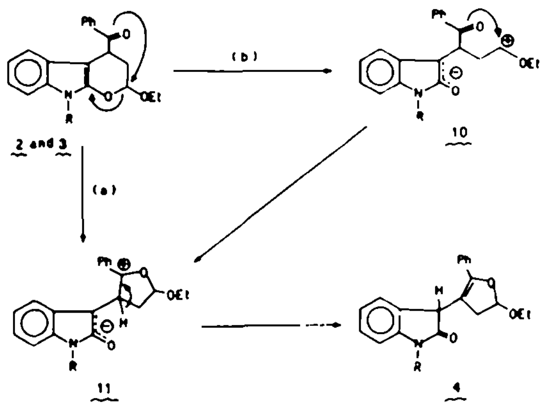


Scheme 4.

been considered. Both **2** and **3** in ethyl vinyl ether, under conditions comparable to the experimental reaction, were stable and **4** was never found. **4** can only be obtained from both **2** and **3** if these are heated in benzene at 140° in a sealed tube or, under milder conditions, with a more polar solvent (CH_3CN) and, for N-acetyl derivatives, in the presence of a trace of acid.

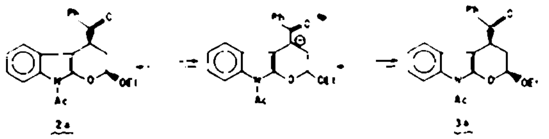
Two possible routes of isomerization **2** or **3**→**4** can be proposed. The first involves an internal nucleophilic attack of the ketonic oxygen atom on the anomeric center at C_2 (Scheme 5, route **a**). Alternatively the large solvent effect supports the presence of an open-chain zwitterionic intermediate **10** (route **b**).

If isomerization follows route **a**, the most favourable situation for attack occurs if the adduct has a trans configuration. However both in benzene and in acetonitrile the cis adduct **2a** isomerizes faster than the trans one. Therefore route **b** is strongly suggested and the easier isomerization of the cis adduct can be simply rationalized as due to the lower thermodynamic stability of **2a** compared to **3a**.



Scheme 5.

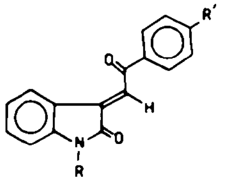
This was demonstrated by equilibration of **2a** and **3a** in the presence of a base. The equilibrium is displaced in favour of **3a** and the intermediate anion (Scheme 6) was shown by incorporation of deuterium.



Scheme 6.

The formation of **4** under kinetically controlled conditions implies the presence of a zwitterionic intermediate **10**. This can collapse to the final adduct as described in the Scheme 5 (route **b**) for the isomerization of **2** and **3** into **4**. If this is true, the formation of **4** depends upon the nucleophilicity of the ketonic oxygen atom, which of course can be varied by substitution of the adjacent phenyl ring.

We have therefore investigated the reaction of both oxindolidene-(p-methoxy- and p-nitro)acetophenones.



1d: R = MeCO—; R' = OMe
e: = MeCO—; = NO_2
f: = H— ; = OMe
g: = H— ; = NO_2
h: = Me— ; = OMe
i: = Me— ; = NO_2

Adducts **2**, **3** and **4** are formed, their yields are shown in Table 3 and IR spectra are reported in Table 4.

Table 3.

1	Adducts total yield %	2%	3%	4%[a]
d	90	76	8	6
e	80	67	13	----
f	71	50	----	21
g	41	34	14	----
h	71.5	35	7.5	29
i	29	17	12	----

[a] Diastereomeric mixture.

Table 4. IR spectra of starting products and adducts

Compd	$\nu_{C=C}$ exocyclic	$\nu_{C=C}$ dihydropyr.	$\nu_{C=O}$ lactam	$\nu_{C=O}$ ketone	$\nu_{C=O}$ acetyl
1d	1627 w	------	1742 s	1657 s	1717 m
2d	absent	1640 s	absent	1672 s	1702 s
3d	absent	1649 s	absent	1678 s	1702 s
4d	absent	absent	1759 s	absent	1705 s
1e	1612 m	------	1750 s	1665 s	1700 s
2e	absent	1649 s	absent	1699 s	
3e	absent	1639 s	absent	1698 s	1711 s
1f	1629 m	------	1715 s	1659 s	------
2f	absent	1635 m	absent	1672 s	------
4f	absent	absent	1705 s	absent	------
1g	1625 w	------	1725 s 1705 w	1669 s	------
2g	absent	1640 m	absent	1698 s	------
3g	absent	1633 m	absent	1690 s	------
1h	1630 m	------	1721 s 1714 s	1662 s	------
2h	absent	1633 m	absent	1678 s	------
3h	absent	1636 m	absent	1672 s	------
4h*	absent	absent	1720 s*	absent	------
1i	1622 m	------	1712 s	1662 s	------
2i	absent	1638 s	absent	1701 s	------
3i	absent	1629 s	absent	1687 s	------

*Film, broad band.

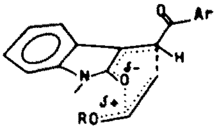
The methoxy-substitution causes a slight but nevertheless significant increase in the yield of 4. The nitro-substitution has a greater effect since it weakens the nucleophilicity of the oxygen (or alternatively destabilizes the intermediate 11) so that the zwitterion 10 cannot undergo ring closure to the furan derivative.

Two opposite conclusions regarding the mechanism can be based on (a) the cis dihydropyran isomer predominates over the trans one and if this fact is not the result of thermodynamic control, it is generally considered as proof of a preferred endo transition state in a Diels-Alder-like reaction; (b) since the dihydrofuran adducts 4 were shown to be primary reaction products they can only be formed via a zwitterionic intermediate.

Analogous behaviour was found previously in the reaction between arylidene-isoxazolones or -pyrazolones and dihydropyran.[8] When no secondary steric interaction occurs, the most predominant adduct is the thermodynamically less stable all-cis isomer, but a certain amount of product involving a zwitterionic intermediate was sometimes found.

The old approach in terms of competition between two opposite mechanisms seems too schematic and not flexible enough to represent the various aspects of the heterodiene syntheses.

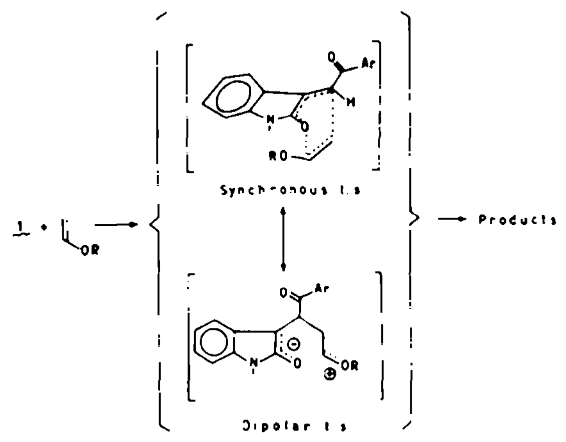
A better rationalization of these cycloadditions can be proposed in terms of a transition state with partial charge separation.



An alternative way to represent the transition state drawn above is to describe it as a hybrid where the zwitterion 10 contributes as a hyperconjugated structure[9] (Scheme 7). its contribution can vary depending upon solvent, substituents and experimental conditions and, exceptionally, can become overwhelming.[10] We will discuss this point later.

The recent perturbation approach to cycloadditions[11,12] is consistent with the above proposed rationalization.

Heterodiene syntheses involving α,β-unsaturated carbonyl compounds are $HOMO_{olefin}/LUMO_{carbonyl}$ control-



Scheme 7.

led.[11] If the olefin HOMO has a higher energy or the carbonyl LUMO is lowered the energy separation of the frontier orbitals decreases and the reaction becomes easier.[14]

Alkylvinylethers have ionization potentials (i.p.) in the range 8·68 (CH_2=CH–O*t*.But) – 8·93 (CH_2=CH–OMe)[*] eV.[15] Dihydropyran has a particularly low i.p.: 8·54 eV.[15] Since the energy of the HOMOs corresponds, in accordance with Koopmans' theorem, to the negative of the i.p., HOMO energies increase from alkylvinylethers to dihydropyran (Fig. 1, **a**).

The same effect on the separation of frontier orbitals can be obtained with the α,β-unsaturated carbonyl compound.

Simple considerations of substituent effects conclude that an electron-withdrawing group will raise both the i.p. and the electron affinity of the α,β-unsaturated carbonyl compound; therefore the presence of the β-benzoyl group will lower the carbonyl LUMO energy (Fig. 1, **b**).

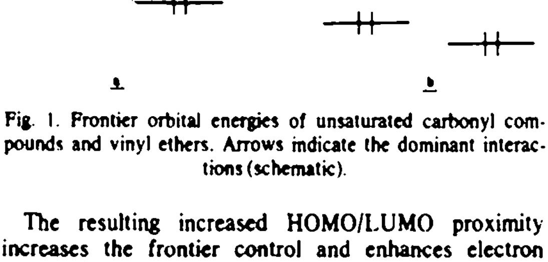


Fig. 1. Frontier orbital energies of unsaturated carbonyl compounds and vinyl ethers. Arrows indicate the dominant interactions (schematic).

The resulting increased HOMO/LUMO proximity increases the frontier control and enhances electron transfer.[16]

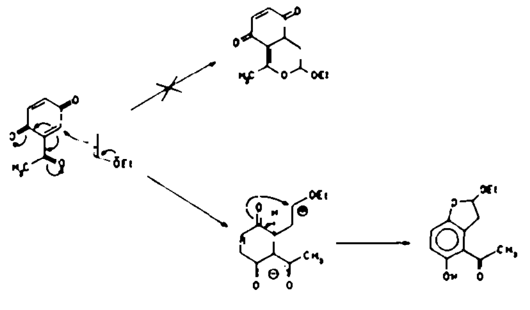
The favourable n–π interaction with high π charge on the β carbon of the dihydropyran ether[17] and the electron-attracting substituent on the β-position of the C=C–C=O system increase the asymmetry of the double bonds of the dienophile and of the heterodiene respectively.

Asymmetry of the reagents and high frontier control both contribute to the development of non-synchroneity of the reaction.[11]

With this approach, non-synchroneity can be explained in terms of the different timing of C–C and C–O bond-closure of the transition state. If the stability of the C·····O bond is in competition with its rupture, e.g. due to thermal vibrations etc., the statistical distribution between "retention" and "rupture" depends upon the bond energy, the stabilization of the open intermediate and the experimental conditions.

Therefore the alternative "synchronous"/"two-step" mechanism of a reaction loses much of its competition since variation of the experimental conditions or a small subsitutent effect can show up a previously-masked gap.

A remarkable analogy with the behaviour of oxindolideneacetophenones was found with α,β-unsaturated carbonyl derivatives which also have a p-quinone system. They react with ethyl vinyl ether[10] but no 1,4-cycloadduct is formed (Scheme 8).

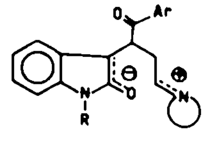


Scheme 8.

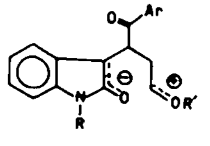
A zwitterionic intermediate is formed which is stabilized to a large extent by resonance. Electrophilic attack at the oxygen atom not involved in the stabilization, followed by proton loss and gain, gives a benzofuran derivative.

The large stabilization involved in the intermediate and the gain in aromaticity,[11] rationalize the overwhelming contribution of the zwitterion to the transition state and the yield of the dihydrofuran adduct as the only reaction product.

A final point requires some remarks. If the fate of the transition state depends upon the stability and the electronic characters of the zwitterionic structure, the stabilization as the immonium ion of A allows either a proton loss and gain to give open-chain enamines,[4,18] or an electrophilic attack on the 3-position of the oxindole ring to give spiro-cyclobutane derivatives.[3]



A



B

The lower stabilization as the oxonium ion of **B** does not allow the above reported reaction, it can only undergo a nucleophilic attack from the ketonic oxygen atom (when

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[*] Determined by charge transfer complexes: a recent photoelectron spectroscopy determination gave the i.p. of methylvinylether as 9·05 eV (H. Bock, G. Wagner, K. Wittel, J. Sauer and D. Seebach, *Chem. Ber.* 107, 1869 (1974).

present and sufficiently reactive) and dihydrofuran derivatives **4** are formed.

The contribution of **B** to the transition state is of course much lower than that of **A**.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra (Nujol mulls) were determined on a Perkin-Elmer 257 spectrophotometer. NMR spectra were obtained by Dr. Anna Gamba Invernizzi on a Perkin-Elmer R12A spectrophotometer (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Microanalyses were performed by Dr. Lucia Maggi Dacrema.

3-Oxindolideneacetophenones 1

These were prepared by the reported method[19] from isatin or 1-methyl-isatin[20] and the appropriate acetophenone. **1a,d,e** were obtained by acetylation of the corresponding unsubstituted derivative.[21] The products reported in Table 5 were obtained.

Table 5.

Compd	Fisical aspect (yield %)	m.p. (solvent)	Elementary analisis or m.p. and literature references	NMR Vynilic proton
1a	yellow needles (60)	121-122° (EtOH)	lit[21] 121° (EtOH)	7.82[3]
1b	orange needles (71)	194-195° (EtOH)	lit[19a] 193-194° (EtOH)	7·89[3]
1c	red needles (65)	127-128° (EtOH)	lit[19a] 127-128° (EtOH)	7·89[3]
1d	yellow needles (58)	124-125° (EtOH)	found: C,71·50; H,4·82; N,4.47 for $C_{19}H_{15}NO_4$ calc: C,71·02; H,4·71; N,4·36%	7.71
1e	yellow needles (70)	171-172° (AcOEt)	found: C,64·75; H,3·70; N,8·61 for $C_{18}H_{12}N_2O_5$ calc: C,64·28; H,3·60; N,8·33%	7·81
1f	orange needles (75)	201-202° (dioxane)	lit[19a] 201° (EtOH)	7.83
1g	red crystals (82)	241-242° (dioxane)	found: C,65·47; H,3·65; N,9·80 for $C_{16}H_{10}N_2O_4$ calc: C,65·30; H,3·43; N,9·52%	*
1h	orange needles (82)	124-125° (EtOH)	lit[19b] 119-123° (EtOH)	7·81
1i	deep red platelets (74)	242-243° (dioxane)	found: C,65·74; H,3·96; N,9·22 for $C_{17}H_{12}N_2O_4$ calc: C,66·23; H,3·92; N,9·09%	*

*1g,i were not measured, owing to their very low solubility.

Reaction of 1 *with ethylvinylether. General method*

A suspension of **1** in freshly-distilled ethyl vinyl ether was heated on an oil bath at 100° in a Paar bomb. Starting from **1a, d, e**, after cooling, pure or nearly pure **2** were collected and washed with diethyl ether. Crystalline dihydropyran mixtures **2** and **3** were obtained as further crops after standing and cooling of the concentrated mother liquors.* Finally the oily residue was chromatographed (column-length 80 cm, diameter 4·5 cm; Kieselgel Merck 0·06–0·2; cyclohexane-AcOEt 70/30 as eluant) and two fractions were obtained: pure **4** (first fraction) and the mixture of **2** and **3**.

Starting from **1 b, c, f, h**, the solution was evaporated to dryness at room temp. The residue was triturated with diethyl ether and pure **2** was filtered off. The oily residue, obtained by evaporation of the mother liquors, was chromatographed as reported above. Dihydropyran mixture **2** and **3** was obtained as the first fraction, followed by pure dihydrofurans **4**.

Starting from **1 g, i**, after cooling, unreacted **1** (66 and 42% respectively) was collected. The deep-coloured mother liquors were treated as described for the previous series and dihydropyran mixtures only were obtained. Pure **2** and **3** were obtained by fractional crystallization.

The ratio of **2** versus **3** was calculated by NMR from an homogeneous sample of isomers (regions of the CH_3 in the ethoxy group or H_2 and H_4 signals of the dihydropyran ring). Reaction time, ratio of the reagents and physical characteristics of the adducts are reported in Table 6. The main values for the NMR spectra of **2**, **3** and **4** are summarized in Tables 7 and 8.

Dihydrofurans 4 *starting from dihydropyrans* 2 *and* 3. *General method*

A solution of **2** or **3** (2 mmoles) in distilled acetonitrile or benzene (20 ml) was heated and the gradual disappearance of the starting product and the formation of **4** was followed (TLC, cyclohexane : AcOEt 70/30). Alternatively the decrease of the C=O ketonic band and the increase of the C=O lactamic band in the IR spectrum of the CH_3CN solution (0·1 ml of the starting solution to 2·5 ml, thickness 0·1 mm) was followed. Pure **4** was obtained by evaporation of the solution and purified by fractional crystallization or by column chromatography if starting material is still present. The conditions used for each product are summarized in Table 9.

Isomerization of 2a *into* 3a

To a solution of **2a** in C_6D_6 (0·35 mol) a drop of Et_3N was added and the isomerization was monitored by NMR (35°). After 48 h the equilibrium **2a**/**3a** was reached and the ratio 40 : 60 was evaluated by inspection of 2-H signal of **3a** versus the sum of 4-H and 2-H signals of **3a** and **2a** respectively. If the NMR experiments are run in $(CD_3)_2CO$ with a drop of Et_3N and D_2O, after 24 h at 35° the 4-H signals of **2a** and **3a** disappeared and only the 2-H signals

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*Final crops contained a by-product (~2% yield) which we shall consider elsewhere.

Table 6.

Compd	Reaction time (ratio mmole 1/ ml vinylether)	Physical aspect (yield %)	m.p. (solvent)	Elementary analysis		
2a	45' (4/12)	White platelets (76)	154-155° (EtOH)		found:	C,72.77; H,5.80; N,3.97
3a		White prisms (8)	131-132° (MeCN)		found:	C,72.65; H,5.75; N,3.90
4a		White crystals (5)	133-134° (EtOH)		found:	C,72.79; H,5.85; N,3.96
				for $C_{22}H_{21}NO_4$	calc:	C,72.71; H,5.82; N,3.85%
2b	14-17 h (8/24)	Pale yellow crystals (35-60)	140-141° (benzene)		found:	C,75.03; H,6.03; N,4.51
4b		Soft white needles (12-18)	159-160° (EtOH)		found:	C,74.63; H,5.92; N,4.58
				for $C_{20}H_{19}NO_3$	calc:	C,74.74; H,5.96; N,4.36%
2c	22 h (4/12)	White crystals (50)	115-116° (dIPE)		found:	C,74.99; H,6.36; N,4.16
3c		White prisms (9)	114-115° (EtOH)		found:	C,75.01; H,6.37; N,4.22
4c		Pale yellow oil (16)	(pet.eth.)		found:	C,74.80; H,6.34; N,4.33
				for $C_{21}H_{21}NO_3$	calc:	C,75.20; H,6.31; N,4.18%
2d	1 h (4/12)	White crystals (76)	123-124° (EtOH)		found:	C,69.97; H,5.90; N,3.62
3d		White prisms (8)	175-176° (EtOH)		found:	C,69.90; H,5.95; N,3.70
4d		White needles (6)	139-140° (MeCN)		found:	C,70.00; H,6.00; N,3.65
				for $C_{23}H_{23}NO_5$	calc:	C,70.21; H,5.89; N,3.56%
2e	3 h (4/12)	Yellow crystals (67)	171-172° (benzene)		found:	C,65.13; H,4.95; N,6.84
3e		Orange needles (13)	184-185°dec. (MeCN)		found:	C,64.85; H,4.99; N,6.80
				for $C_{22}H_{20}N_2O_6$	calc:	C,64.70; H,4.94; N,6.86%
2f	47 h (16/24)	White platelets (50)	155-156° (benzene)		found:	C,72.01; H,6.23; N,4.04
4f		White needles (21)	154-155° (EtOH)		found:	C,71.98; H,6.09; N,4.06
				for $C_{21}H_{21}NO_4$	calc:	C,71.78; H,6.02; N,3.99%
2g	65 h** (8/24)	Red prisms (33.6)	153-155° (benzene)		found:	C,65.47; H,5.14; N,7.88
3g		Soft yellow needles (14.4)	182-183° (benzene)		found:	C,65.66; H,5.20; N,7.78
				for $C_{20}H_{18}N_2O_5$	calc:	C,65.56; H,4.95; N,7.65%
2h	12 h (4/12)	White needles (35)	129-131° (dIPE)		found:	C,72.04; H,6.30; N,3.87
3h		White prisms (7.5)	150-152° (EtOH)		found:	C,72.12; H,6.42; N,3.98
4h		Pale yellow oil (29)	*		found:	C,72.20; H,6.41; N,3.91
				for $C_{22}H_{23}NO_4$	calc:	C,72·31; H,6·34; N,3·83%
2i	96 h** (8/24)	Orange crystals (17·4)	161-162° (benzene)		found:	C,66·24; H,5.27; N,7·38
3i		Amaranth platelets (11·6)	153-154° (benzene)		found:	C,66·25; H,5·25; N,7·16
				for $C_{21}H_{20}N_2O_5$	calc:	C,66·30; H,5·30; N,7·37%

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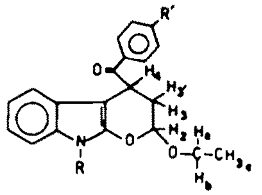
[*] The oil was treated in warm petroleum ether, the solvent was decanted from the cooled solution and oily residue dried 4h at 100°, 0·4 mm pressure.

[**] Longer reaction times caused tarry mixtures and lower yields of the isolated adducts.

Table 7. NMR of



Compd[a]	Chemical shifts H_2	H_3	$H_{3'}$	H_4	H_a	H_b	H_c	R	R'	Aromatics	Coupling constants[b] J_{23}	$J_{23'}$	J_{34}	$J_{3'4}$	$-J_{33'}$	$-J_{ab}$	$J_{c(vic)}$
2a	5.35	2.42		4.60	3.90	3.59	1.17	Ac 2.62	H (arom)	6.8–8.5	7.8		13.6		----	9.1	7.0
3a	5.57	2.28		4.95	3.93	3.71	1.24	Ac 2.63	H (arom)	6.7–8.5	6.9		14.4		----	9.2	7.0
2b	5.23	2.38		4.61	3.89	3.54	1.11	H	H (arom)	6.7–8.15	8.4		14.1		----	9.3	6.9
2b[c]	5.38	2.25	2.36	4.81	3.89	3.61	1.10	H 9.88	H (arom)	6.7–8.2	5.77	2.25	6.83	6.72	13.37	9.7	6.9
2c	5.35	2.43		4.71	3.97	3.62	1.18	Me 3.56	H (arom)	6.8–8.1	8.0		13.9		----	9.0	6.9
3c	5.60	2.28		5.05	3.96	3.63	1.22	Me 3.56	H (arom)	6.8–8.3	6.6		13.7		----	9.0	7.0
2d	5.35	2.41		4.63	3.94	3.63	1.19	Ac 2.61	OMe 3.84	6.8–8.55	8.7		14.7		----	9.3	6.8
3d	5.59	2.30		4.91	3.95	3.64	1.24	Ac 2.54	OMe 3.87	6.75–8.55	6.9		14.6		----	9.3	7.0
2e	5.46	2.46		4.46	3.86	3.61	1.12	Ac 2.64	NO_2	6.9–8.55	6.0		11.5		----	9.3	7.0
3e	5.58	2.28		4.90	3.94	3.72	1.24	Ac 2.62	NO_2	6.65–8.45	6.6		14.8		----	9.3	7.1
2f	5.31	2.41		4.68	3.95	3.61	1.16	H	OMe 3.81	6.8–8.1	9.3		15.1		----	9.3	7.1
2f[c]	5.38	2.25	2.38	4.86	3.91	3.62	1.09	H 9.96	OMe 3.84	6.75–8.2	7.17	1.99	8.11	6.63	13.19	9.2	6.8
2g	5.31	2.41		4.41	3.84	3.55	1.06	H	NO_2	6.9–8.4	6.6		11.9		----	9.3	6.9
3g	5.54	2.26		4.95	3.95	3.72	1.22	H	NO_2	6.8–8.5	6.0		14.6		----	9.6	6.9
2h	5.32	2.40		4.71	4.01	3.64	1.20	Me 3.55	OMe 3.80	6.8–8.2	9.3		15.0		----	9.5	6.8
3h	5.58	2.26		4.97	3.95	3.72	1.22	Me 3.54	OMe 3.85	5.8–8.3	6.8		14.3		----	10.0	6.9
2i	5.37	2.42		4.46	3.90	3.58	1.09	Me 3.58	NO_2	6.9–8.35	6.6		11.9		----	9.1	7.1
3i	5.58	2.27		4.97	3.98	3.63	1.24	Me	NO_2	5.7–8.55	6.4		14.6		----	9.3	7.0

[a] $CDCl_3$ as solvent

[b] The reported values are the sum $J_{23}+J_{23'}$ or $J_{34}+J_{3'4}$; except for 2b and 2f.

[c] $(CD_3)_2CO$ as solvent, completed by LAOCOON 3 program, used on UNIVAC 1108 computer. RMS value in the last iteration less than 0.10.

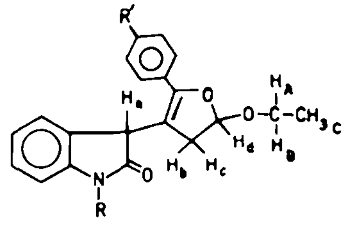
(5·5–5·8 δ) of both cis and trans isomers are present. Using this technique reasonable quantities of **3a** can be obtained boiling 9h a solution of **2a** in benzene in the presence of Et_3N.

Hydrolytic cleavage of 2, 3 *and* 4

β - Benzoyl - β - (1 - acetyl - 3 - oxindolyl)propionaldehyde **5a**. (a) HCl 0·6 N (0·2 ml) was added at room temp to a stirred solution of **2a** (0·36 g; 1 mmole) in acetone (20 ml). When the starting product disappeared (TLC, few min), the solution was evaporated to dryness. Any attempt to crystallize the white amorphous residue was unsuccessful. The NMR spectrum ($CDCl_3$) showed it to be a mixture of two diastereoisomers in the ratio 79:21 calculated from the methyl signal of the acetyl group. Major isomer: 2·68 3H s (N–Ac); 2·95 2H d (J = 6·6) (–CH_2–CHO); 3·85 1H d (J = 2·7) (CH oxindole); 4·81 1H dt (J = 2·7 and 6·6) (CH–COPh); 9·65 1H s (CHO); 7·0–8·3 9H m (aromatic). Minor isomer (same signals): 2·47; 2·95 (6·6); 4·06 (6·6); 4·58 q (6·6); 9·69; 7·0–8·3.

(b) Starting from **3a** and **4a** and following the above method, an analogous result was obtained.

Table 8. NMR of



Compd[a]	Chemical shifts										Coupling constants[b]				
	H_a	H_b	H_c	H_d	H_A	H_B	H_C	R	R'	Aromatics	J_{bd}	J_{cd}	$-J_{bc}$	$-J_{AB}$	$J_{C(vic)}$
4a	4.84	2.5[c]		5.03	3.94	3.66	1.25	Ac 2.71	H (arom)	7.05–8.4	10.5		----	9.9	7.0
4b[d]	4.68	2.38	2.62	5.59	3.89	3.60	1.19	H 9.45	H (arom)	6.7–8.0	2.71	7.19	15.90	9.8	7.3
4c	4.62	2.4		5.52	3.90	3.55	1.20	Me 3.20	H (arom)	6.7–8.0	10.0		----	10.5	7.2
4d	4.78	2.5[c]		5.57	3.89	3.61	1.21	Ac 2.69	OMe 3.82	6.7–8.4	10.0		----	10.4	7.0
4f[d]	4.66	2.46	2.64	5.59	3.92	3.61	1.20	H 9.60	OMe 3.81	6.8–7.9	2.87	7.03	16.00	10.1	6.9
4h	4.59	2.4		5.51	3.97	3.62	1.18	Me 3.21	OMe 3.80	6.6–8.0	10.0		----	10.3	7.3

[a] $CDCl_3$ as solvent, the reported values concern the major component of the diastereomeric mixture.

[b] The reported values are the sum $J_{bd}+J_{cd}$, except for 4b and 4f.

[c] Partially overlapped by CH_3 of the acetyl group.

[d] Computed by LAOCOON 3 program, used on UNIVAC 1108 computer. RMS value in the last iteration less then 0.10.

β-Benzoyl-β-(3-oxindolyl)propionaldehyde **5b**

HCl 0·6 N (0·2 ml) was added to a stirred solution of **2b** or **4b** (0·32 g; 1 mmole) in acetone (5 ml) at room temp. Stirring was continued until the starting product disappeared (TLC – ≃ 30') and a few ml of $NaHCO_3$ solution were added. The acetone was evaporated under vacuum and the amorphous white solid was filtered off. Any attempt to crystallize the solid was unsuccessful and both IR and NMR are too poorly resolved to be fully interpreted. Nevertheless the main signals and bands are in accordance with the proposed structure.

β-Benzoyl-β-(1-methyl-3-oxindolyl)propionaldehyde **5c**

Starting from **2c**, **3c** or **4c** and following the method described for **5b**, after evaporation of the acetone the emulsion was extracted with diethyl ether (3 × 15 ml). The ethereal solution was evaporated and an oily residue was obtained. Any attempt to purify the oil was unsuccessful and furthermore its IR and NMR were too poorly resolved to be fully interpreted, though generally in accordance with the proposed structure.

β-Benzoyl-β-(3-oxindolyl)propionaldehyde diethyl acetal **6b**

(a) A solution of **2b** (0·32 g; 1 mmole) in anhydrous EtOH (10·0 ml) was refluxed until the starting product disappeared (TLC, ≃ 20 h). The solution was evaporated at room temp under vacuum and a pale yellow oil was obtained. The elemental analysis was obtained from a crude sample dried for 4 h at room temp under 0·1 mm. Any attempt to distil the product caused decomposition (Found: C, 72·07; H, 7·12; N, 4·08. Calc for $C_{22}H_{25}NO_4$: C, 71·91; H, 6·86; N, 3·81%). IR (film): 1710 and 1685 cm^{-1} (C=O lactam and ketone respectively). NMR ($CDCl_3$): 3·77 1H diffuse doublet (CH oxindole); 4·5 2H broad signal (CH–COPh and $CH(OEt)_2$); 1·63 1H and 2·03 1H (J_{gem} = –12·0) (–CH_2–); 3·47 4H unsharp quartet (O–CH_2 of the ethoxy groups); 1·07 3H t (J = 6·6) 1·08 3H t (J = 6·6) (2 CH_3 of the ethoxy groups); 9·6 1H broad signal (NH); 6·7–8·3 9H m (aromatics). Chemical shifts and coupling constants of the –CH_2– group were determined by spin decoupling experiments, which are fully in accordance with the reported structure.

(b) Following the above reported method and starting from **4b** the identical product was obtained.

(c) One drop of 96% H_2SO_4 was added to a cooled and stirred solution of **5b** (0·36 g; 1 mmole) in anhydrous EtOH. After 1 h the solution was evaporated at room temp and the residue was dissolved in diethyl ether and washed with $NaHCO_3$ solution. The ethereal fraction was dried (Na_2SO_4) and after evaporation gave a pale yellow oil, identical in every respect with the previously-described sample. Treating **6b** (0·36 g; 1 mmole) at room temp under stirring with a mixture of AcOH (12 ml) and HCl (0·6 N; 0·8 ml), the aldehyde **5b** was obtained.

β-Benzoyl-β-(1-methyl-3-oxindolyl)propionaldehyde diethyl acetal **6c**

(a) Following the method (a) used to prepare **6b**, white needles of **6c** were obtained from **2c** in nearly quantitative yield, m.p. 112–113° (EtOH) (Found: C, 72·45; H, 7·16; N, 3·68. Calc for $C_{23}H_{27}NO_4$: C, 72·42; H, 7·13; N, 3·67%). IR: 1718 and 1685 cm^{-1} (C=O lactam and ketone respectively). NMR ($CDCl_3$): 3·74 1H d (J = 2·5) (CH oxindole); 4·50 1H m (J = 2·5, 5·3 and 7·9) (CH–COPh); 1·64 1H and 2·11 1H (J_{gem} = –13·9) (–CH_2–); 4·45 1H t (J = 5·7) ($CH(OEt)_2$); 1·07 3H t (J = 7·0) and 1·09 3H t (J = 7·0) (2

Table 9.

Starting compound	Solvent	Temp °C	Appearance of **4** after:	Reaction time	Final composition	
					2 or **3**	**4**
2a	CH_3CN	reflux	20 h	5 d[a]	73.5	7
2a	CH_3CN[b]	reflux	fast	22 h	----	57
2a	benzene	140[c]	----	5 d	~ 50[d]	traces
3a	CH_3CN	reflux	96 h	10 d[a]	65	6
3a	CH_3CN[b]	reflux	fast	22 h	----	60
3a	benzene	140[c]	----	10 d[a]	~30[d]	traces
2b	CH_3CN	reflux	2 h	18-20 h	----	~100
2b	benzene	140[c]	----	25-30 h	----	60[d]
2c	CH_3CN	reflux	2 h	10-12 h	----	~100
2c	benzene	140[c]	----	24 h	----	~65[d]
3c	CH_3CN	reflux	2 h	10-12 h	----	~100
3c	benzene	140[c]	----	24 h	----	~65[d]

[a] Longer reflux causes the formation of oily by-products and the separation of the crystalline products becomes very difficult.

[b] Added with 0.5 ml of p.toluensulfonic acid (0.0025 M - solution in CH_3CN).

[c] In a Paar bomb.

[d] Oily by-product not identified.

CH_3 of the ethoxy groups); 3·44 2H and 3·47 2H (2 CH_2 of the ethoxy groups); 3·23 3H s (N–CH_3); 6·6–8·3 9H m (aromatic). Some chemical shifts and coupling constants were determined by spin decoupling experiments which are fully in accordance with the reported structure.

(b) Following the above described method, by starting from **3c**, white needles were obtained, in nearly quantitative yield, identical with the previously-described **6c**.

(c) Analogously, but starting from **4c**, white needles of **6c** were obtained in 60–65% yield.

(d) Following the method (c) described for **6b**, **5c** gave directly a white solid which, after 1 h, was filtered off and washed with water. A second crop of **6c** was obtained evaporating the mother liquors. Total yield 90%. Treating **6c** with a mixture of AcOH and HCl, **5c** was reobtained.

2-*Phenyl-3-(3-oxindolyl)furan* **7b**

(a) A solution of **4b** (0·32 g; 1 mmole) in dry benzene was refluxed with a trace of p-toluenesulphonic acid until the starting material disappeared (TLC). The cooled solution was washed with $NaHCO_3$ soln and the residue obtained after evaporation was chromatographed (Kieselgel merck 0·05–0·2; cyclohexane AcOEt 70/30). White crystals of **7b** were obtained in 60% yield m.p. 197–199° (EtOH) (Found: C, 78·15; H, 4·81; N, 5·19. Calc for $C_{18}H_{13}NO_2$: C, 78·53; H, 4·76; N, 5·09%). IR: 1708 cm^{-1} (C=O lactam). NMR (DMSO): 4·91 1H s (CH oxindole); 5·99 1H d (J = 1·8) (–CH=furan); 7·65 1H d (J = 1·8) (=CH–O– furan); 6·65–7·95 9H m (aromatic). Spin decoupling experiments support the assignment of the furan protons.

(b) By heating **4b** above its m.p. under nitrogen a lower yield of **7b** (~ 40%) was obtained.

(c) A solution of **5b** (0·29 g; 1 mmole) in AcOH (5·0 ml) and HCl 4 N (4·0 ml) was gently refluxed for 50 min and steam-distilled. The cloudy solution was neutralized ($NaHCO_3$) and extracted with diethyl ether. After evaporation of the ethereal soln, the residue was chromatographed as described under (a) and white crystals of **5b** were obtained in 45% yield.

2-*Phenyl-3-(1-methyl-3-oxindolyl)furan* **7c**

(a) Following the method (a) described for **7b**, pale yellow crystals of **7c** were obtained in 48% yield from **4c**; m.p. 145–147° (EtOH) (Found: C, 78·46; H, 5·25; N, 5·00. Calc for $C_{19}H_{15}NO_2$: C, 78·87; H, 5·23; N, 4·84%). IR: 1718 cm^{-1} (C=O lactam). NMR ($CDCl_3$): 4·85 1H s (CH oxindole); 5·94 1H d (J = 1·8) (–CH= furan); 7·82 1H d (J = 1·8) (=CH–O– furan, determined by decoupling); 3·23 3H s (N–CH_3); 6·75–8·0 9H m (aromatic).

(b) A lower yield of **7c** was obtained by heating **4c** at 150–160° under N_2.

(c) As described for **7b** (method c), pale yellow crystals of **7c** were obtained in 48% yield from **5c**.

2-*Ethoxy-4-benzoyl-9-acetylpyrano[2,3-b]indole* **8a**

A suspension of **1a** (2·91 g; 10 mmole) in ethoxyethyne[22] (5·0 ml) was stirred for 48 h at room temp. The yellow-coloured precipitate was filtered off and washed several times with diethyl ether until a white solid was obtained (1·7 g; 47% yield). The ethereal mother liquors contained yellow coloured by-products whose structures will be reported elsewhere. Pure **8a**: soft white needles, m.p. 183–185° (EtOH/AcOEt 1 : 1). (Found: C, 73·26; H, 5·32; N, 4·02. Calc for $C_{22}H_{19}NO_4$: C, 73·11; H, 5·30; N, 3·88%). IR: 1720 and 1685 cm^{-1} (C=O acetyl and ketone respectively). NMR ($CDCl_3$): 5·25 1H d (J = 3·8) (–CH= pyran); 4·18 1H d (J = 3·8) (CH–COPh pyran); 3·88 2H q (J = 7·0) (OCH_2); 2·70 3H s (N–Ac); 1·30 3H t (J = 7·0) (CH_3 of ethoxy group); 6·85–8·55 9H m (aromatic).

Catalytic hydrogenation of **8a**

A suspension of **8a** (0·54 g; 1·5 mmol) in dioxan (30 ml) was hydrogenated at room temp and atmospheric pressure in the presence of C/Pd 10% (0·2 g). After the uptake of 51 ml H_2, the catalyst was filtered off and the solution was evaporated. The oily residue was chromatographed (Kieselgel H Merck; cyclohexane/AcOEt 70:30) and two fractions were obtained. First fraction: pale yellow oil (0·22 g; b.p. 120–122°/0·2 mmHg) identified as 1 - phenyl - 2 - (1 - acetyl - 3 - oxindolyl) - 4 - ethoxybutan - 1 - one **9a** (Found: C, 71·67; H, 6·45; N, 3·85. Calc for $C_{22}H_{23}NO_4$: C, 72·21; H, 6·34; N, 3·83%). IR (film): broad bands at 1760, 1715 and 1687 cm^{-1} (C=O lactam, acetyl and ketone respectively). NMR ($CDCl_3$): 4·53 1H dt (J = 3·3 and 6·9) (CH–COPh); 3·83 1H d (J = 3·3) (CH oxindole); 3·40 2H q (J = 6·8) (OCH_2); 3·36 2H t (J = 6·7) (CH_2–OEt); 2·70 3H s (N–Ac); multiplet centred at 2·2 2H (CH–CH_2–CH_2O); 1·13 3H t (J = 6·8) (OCH_2–CH_3); 6·95–8·3 9H m (aromatics). Spin decoupling experiments are fully in accordance with the reported structure. The second fraction gave white platelets (0·17 g; 31%) identical (IR, NMR and m.m.p.) with the previously-described cis dihydropyran isomer **2a**.

Acknowledgements—The authors are indebted to Prof. P. Grünanger for helpful discussions and suggestions, and to the Consiglio Nazionale delle Ricerche (CNR, Rome) for financial support.

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