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HETERODIENE SYNTHESES—IX[1]

POLAR CHARACTER OF THE THERMAL REARRANGEMENT OF THE ADDUCTS FROM 3-OXINDOLIDENEACETOPHENONES AND ENAMINES

G. TACCONI, F. MARINONE, A. GAMBA and G. DESIMONI
Istituto di Chimica Organica dell'Università, 27100 Pavia, Italy

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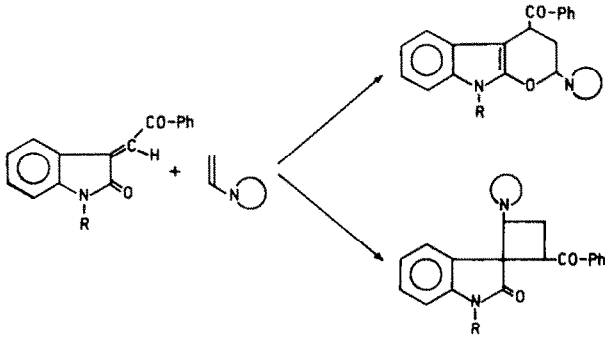
Abstract—The cyclic adducts resulting from the reaction between N-substituted 3-oxindolideneacetophenones and enamines undergo thermal rearrangement in $CDCl_3$ at 35°. If the adducts originate from the β-dimethyl substituted enamine, they revert to the starting materials. In contrast the β-monomethyl substituted adducts are transformed into Michael-type enamines. Both classes of adducts react with tetracyanoethylene to give spirocyclohexane oxindoles. All the reported reactions seem to occur through the same intermediate with a zwitterionic character.

IN A previous paper[2] we have shown that electronic control of the reaction between 3-oxindolideneacetophenones and enamines can give rise to either 1,2- or 1,4-cycloaddition (Scheme 1).

SCHEME 1



The delocalization of the oxindolic nitrogen lone pair on electron-attracting substituents results in dihydropyran derivatives, whereas, if the electron-releasing character of the nitrogen substituent forces the delocalization of the same lone pair onto the α,β-unsaturated carbonyl system, the new charge distribution favours the cyclization to spiro-cyclobutane derivatives.

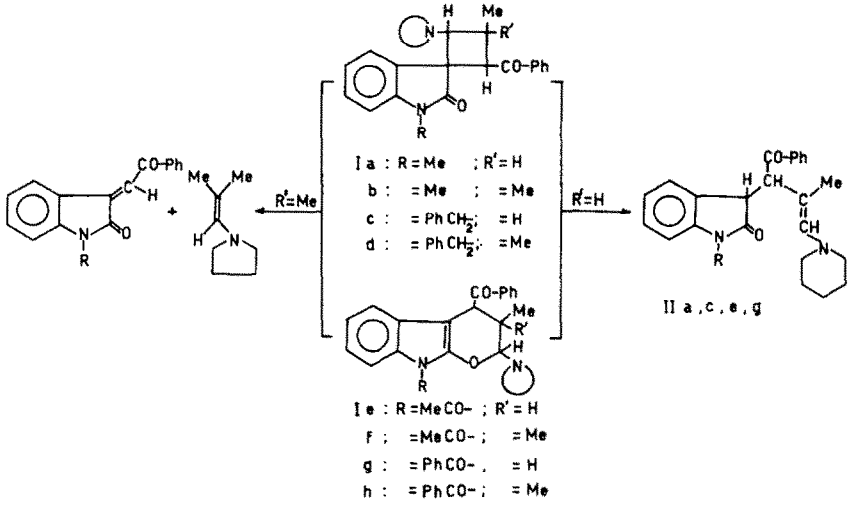
Having shown that border cases follow one or the other type of cycloaddition, we could not exclude that in every case a 1,4-cycloadduct, allowed in terms of W. H. rules,[3] is the kinetically controlled product, which subsequently changes into the thermodinamically more stable 1,2-adduct, whose direct concerted formation would

be forbidden.[3] This point of view, however, contrasts with the mechanism proposed in almost all the previous papers[4a–c] for the reaction between olefines and enamines.

In order to investigate if the conversion of a dihydropyran into the isomeric cyclobutane (fortuitously evidenced for N-benzyldihydropyran[2]) is a general step in these cycloadditions and to gain information on the stability of these adducts, which are stable only at low temp (about − 10°), we have investigated the thermal behaviour of both dihydropyrans and cyclobutanes obtained either from β-monosubstituted or -disubstituted enamines.

The reaction at 35° in $CDCl_3$ for every adduct could be monitored through NMR spectroscopy. The first unexpected results were found not between dihydropyrans and cyclobutanes, but between 3-monomethyl- and 3,3-dimethyl substituted derivatives (Scheme 2).

SCHEME 2



The 3,3-dimethyl substituted adducts (Ib, d, f, h), either dihydropyrans or cyclobutanes, reverted to the starting materials and the NMR spectra of the mixtures were identical with those of the oxindolideneacetophenone[2] and of 1-pyrrolidino-1-isobutene spectra.

The 3-monomethyl substituted adducts (Ia, c, e, g) were transformed into Michael-type enamines (IIa, c, e, g). Their structures were investigated through NMR spectra, which showed the presence of at least two configurational isomers and sometimes a trace of a third (Table 1, resp. isomers A, B and C. For isomer IIe see Fig. 1). The proposed structures are supported by the presence of an olefinic Me group having an allylic coupling with a low field olefinic proton. Unfortunately the differences in the spectral parameters (chem shift and coupling constants) were not significant so as to be able to assign the stereochemistry of the single isomers.

These results are interesting inasmuch as previously only the conversion of a cyclobutane adduct into an enamine was reported by Fleming and Harley-Mason[5]

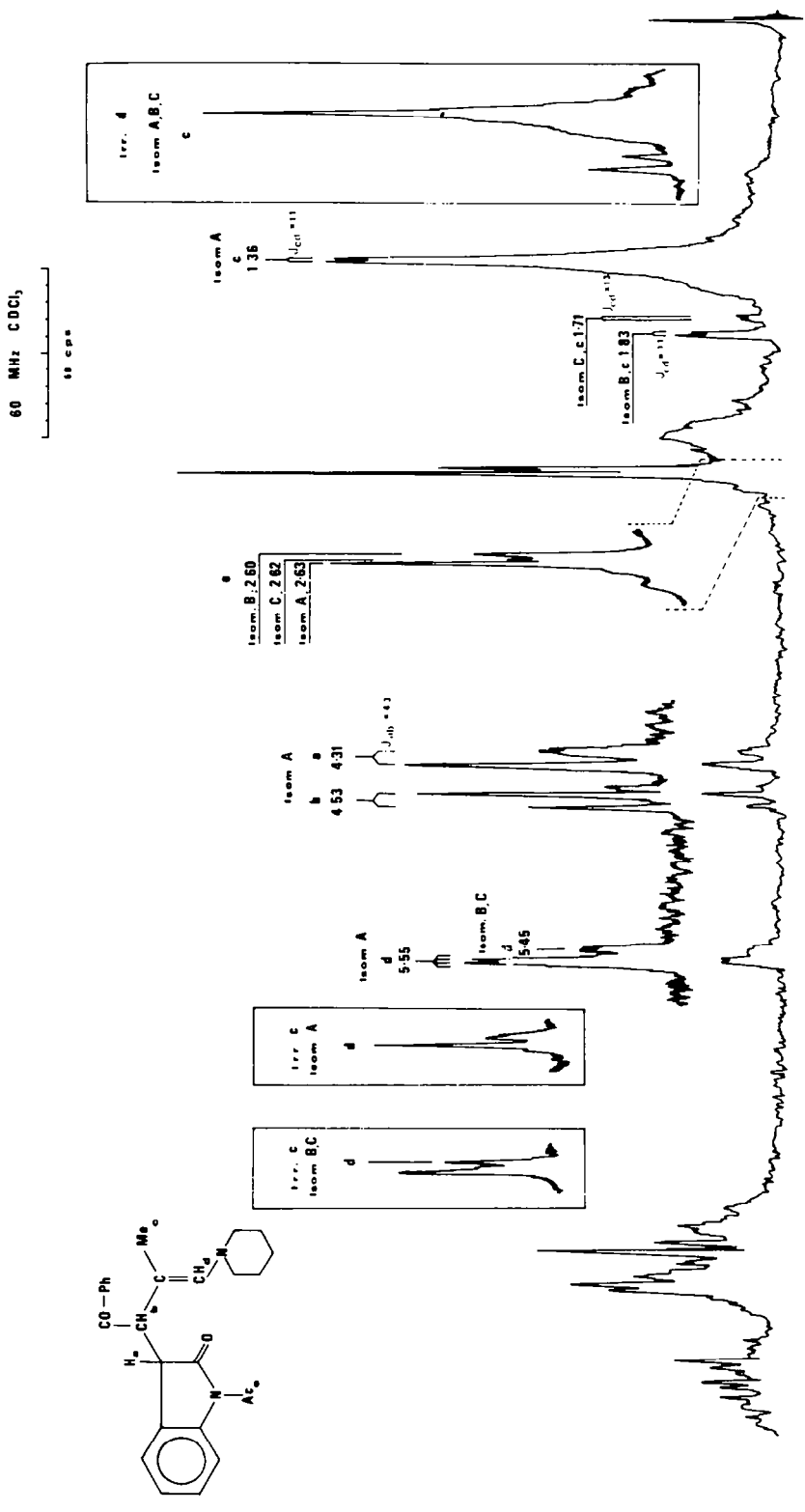
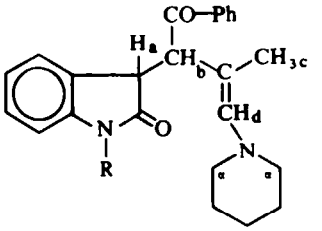


FIG 1. NMR spectrum of 1-piperidyl-3-methyl-3-benzoyl-3[3-(1-acetyl)oxindolyl]propene (IIe) run on a Varian A-60. Spin decoupling spectra run on a Perkin–Elmer R-12 A

TABLE 1*



Compound	Ha	Hb	Hc	Hd	R	Base protons 4 Hα	Base protons 6 H	Aromatics	Yield % ±5%
IIa Isom A	4·18 d J_{ab} 4·0	4·59 d J_{ab} 4·0	1·36 d J_{cd} 1·2	5·50 q J_{cd} 1·2	methyl 3·17 s	2·15–2·80 m	1·15 1·70 m	6·70–8·20 m	75%
IIa Isom B	partially overlapped		1·89 d J_{cd} 1·2	5·50 q J_{cd} 1·2	methyl 3·19 s				25%
IIc Isom A	4·65 d J_{ab} 3·8	4·93 d J_{ab} 3·8	1·42 d J_{cd} 1·0	5·50 q J_{cd} 1·0	benzyl 4·90 s	2·15–2·80 m	1·20–1·70 m	6·85–8·15 m	70%
IIc Isom B	partially overlapped		1·91 d J_{cd} 1·0	5·50 q J_{cd} 1·0					30%
IIe Isom A	4·31 d J_{ab} 4·3	4·53 d J_{ab} 4·3	1·36 d J_{cd} 1·1	5·55 q J_{cd} 1·1	acetyl 2·63 s	2·20–2·80 m	1·20–1·70 m	6·95–8·40 m	65%
IIe Isom B	partially overlapped		1·83 d J_{cd} 1·1	5·45 q J_{cd} 1·1	acetyl 2·60 s				35%
IIe Isom C	partially overlapped		1·71 d J_{cd} 1·3	5·45 q J_{cd} 1·3	acetyl 2·62 s				trace†
IIg Isom A	4·41 d J_{ab} 4·7	4·58 d J_{ab} 4·7	1·47 d J_{cd} 1·0	5·58 q J_{cd} 1·0	benzoyl (arom)	2·00–2·80 m	1·20–1·70 m	7·00–8·30 m	80%
IIg Isom B	partially overlapped		1·83 d J_{cd} 1·0	5·49 q J_{cd} 1·0					20%

* Chem shifts are reported in ppm on the δ scale, coupling constants in cps; $CDCl_3$ was the solvent and TMS the internal standard.
† Traces of a third isomer are present also in the other compounds.

to occur in refluxing dioxane and at room temp by Brannock *et al.*[6] When the present work was nearly complete, examples of thermal rearrangement of dihydropyrans to alkylated enamines were reported by Risaliti *et al.*[7]

In order to clarify the role played by chloroform in the decomposition of the cyclic adducts, the reaction between enamines and oxindolidene derivatives in $CDCl_3$ was investigated.

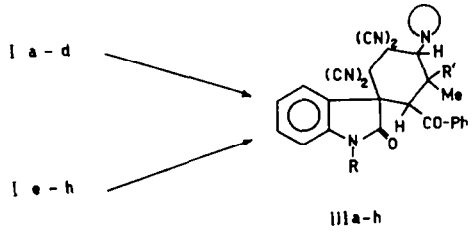
The β-dimethyl substituted enamine does not react under the conditions mentioned and the NMR spectra show only the presence of the starting materials.

The β-monomethyl substituted enamine reacts with N-acetyl and N-methyl oxindolidene derivatives and forms first the cyclic adduct (6-membered or 4-membered respectively), which subsequently behaves as described.

The question now arises whether these reactions, the enamine formation and the reversed cycloaddition, have a concerted mechanism or a two-step mechanism with a zwitterionic intermediate which might give either a σ bond cleavage or, when possible, a proton loss and gain.

Treating the dihydropyran and spiro-cyclobutane adducts (I) with tetracyanoethylene (TCE) under the same experimental conditions used for their ring cleavage, high yields of crystalline adducts were obtained, whose elementary analyses are consistent with 1 : 1-adducts (Scheme 3).

SCHEME 3



These results clearly demonstrate the presence of a zwitterionic intermediate (Fig 2) in the decomposition of all adducts through a two-step pathway already proposed by Fleming.[4a]

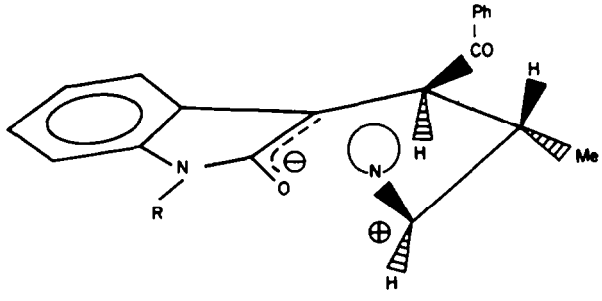


FIG 2.

The alternative direct electrophilic attack of the TCE on the dihydropyran ring[9] is more questionable since the same pathway is not conceivable for cyclobutane adducts. The eventual electrophilic attack on the 4-membered ring should be prevented by the low electronic density of the reacting points due to the relief of conjugation and to the influence of the substituents.

The NMR spectra* of the reaction products of TCE and 3-monomethyl substituted dihydropyran or cyclobutane adducts (Table 2—Fig 3) show that only one isomer is obtained from each reaction and enable the configuration and even the preferred conformation of the cyclohexane fragment to be determined.

The large axial/axial character of the couplings of the protons *a*, *b* and *c* ensures a *trans* stereochemistry with preferred equatorial location of the benzoyl, methyl and piperidyl groups on the cyclohexane ring. The large diamagnetic shift of the *b* axial proton, in addition to the proximity of benzoyl and piperidyl groups, can be rationalized as depending mainly on the influence of the γ-axial cyano group.[8] Apart from some doubtful mechanistic considerations, no conclusion can be drawn about the configuration of the spiro chiral center.

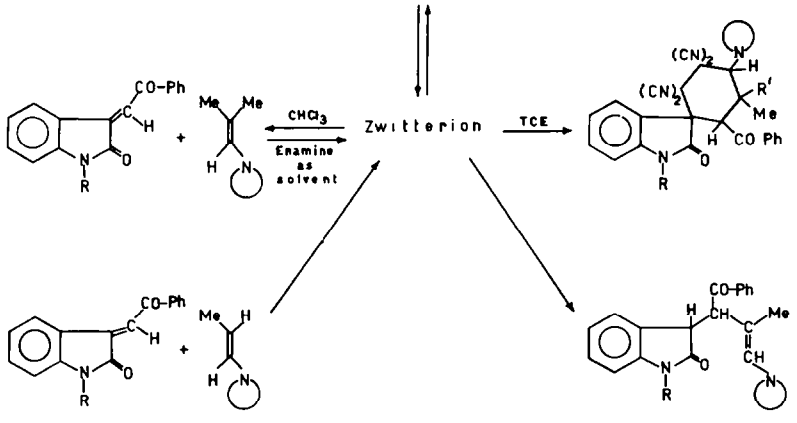
Since TCE reacts with 3-monomethyl substituted adducts (single isomers at least within the limit of the NMR spectroscopy) and gives only one isomer, whose stereochemistry is the same shown by the starting dihydropyran, this suggests an intramolecular stabilization of the zwitterionic structure that prevents any loss of configuration.†

But if we decompose, as previously stated, the same single adduct in the absence of TCE, the NMR spectra of the enamines (II) show the presence of two main isomers with a small amount of a third.

This fact may be ascribed either to a concerted proton shift in the zwitterion followed by equilibration or to an intermolecular mechanism. Both these pathways explain the formation of an isomeric mixture from a pure isomer.

Scheme 4 represents a plausible rationalization of all the hitherto described results.

SCHEME 4

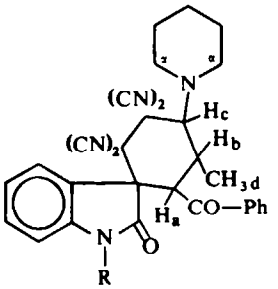


* IIIb, d, g, h were not measured, owing to their very low solubility.

† This also supports the previously suggested[2] 2,3-*trans*-3,4-*trans* configuration for the monomethylcyclobutane adducts

TABLE 2

2



Compd	Ha	Hb	Hc	Hd	R	Base protons 4 Hα	Base protons 6 H	Aromatics
IIIa	4·38 d J_{ab} 10·6	3·83 m J_{ab} 10·6 J_{bc} 11·3 J_{bd} 6·0	3·43 d J_{bc} 11·3	0·97 d J_{bd} 6·0	methyl 3·36 s	2·50–4·00 m	1·40–2·00 m	6·70–7·85 m
IIIc	4·39 d J_{ab} 10·5	3·87 m J_{ab} 10·5 J_{bc} 11·3 J_{bd} 6·0	3·42 d J_{bc} 11·3	0·97 d J_{bd} 6·0	benzyl δ_A 5·06 δ_B 4·99 J_{AB} −16·5	2·30–3·50 m	1·40–2·00 m	6·45–7·80 m
IIIe	4·42 d J_{ab} 10·4	3·70 m J_{ab} 10·4 J_{bc} 11·3 J_{bd} 6·0	3·44 d J_{bc} 11·3	0·97 d J_{bd} 6·0	acetyl 2·84 s	2·00–3·30 m	1·40–1·95 m	6·90–8·30 m

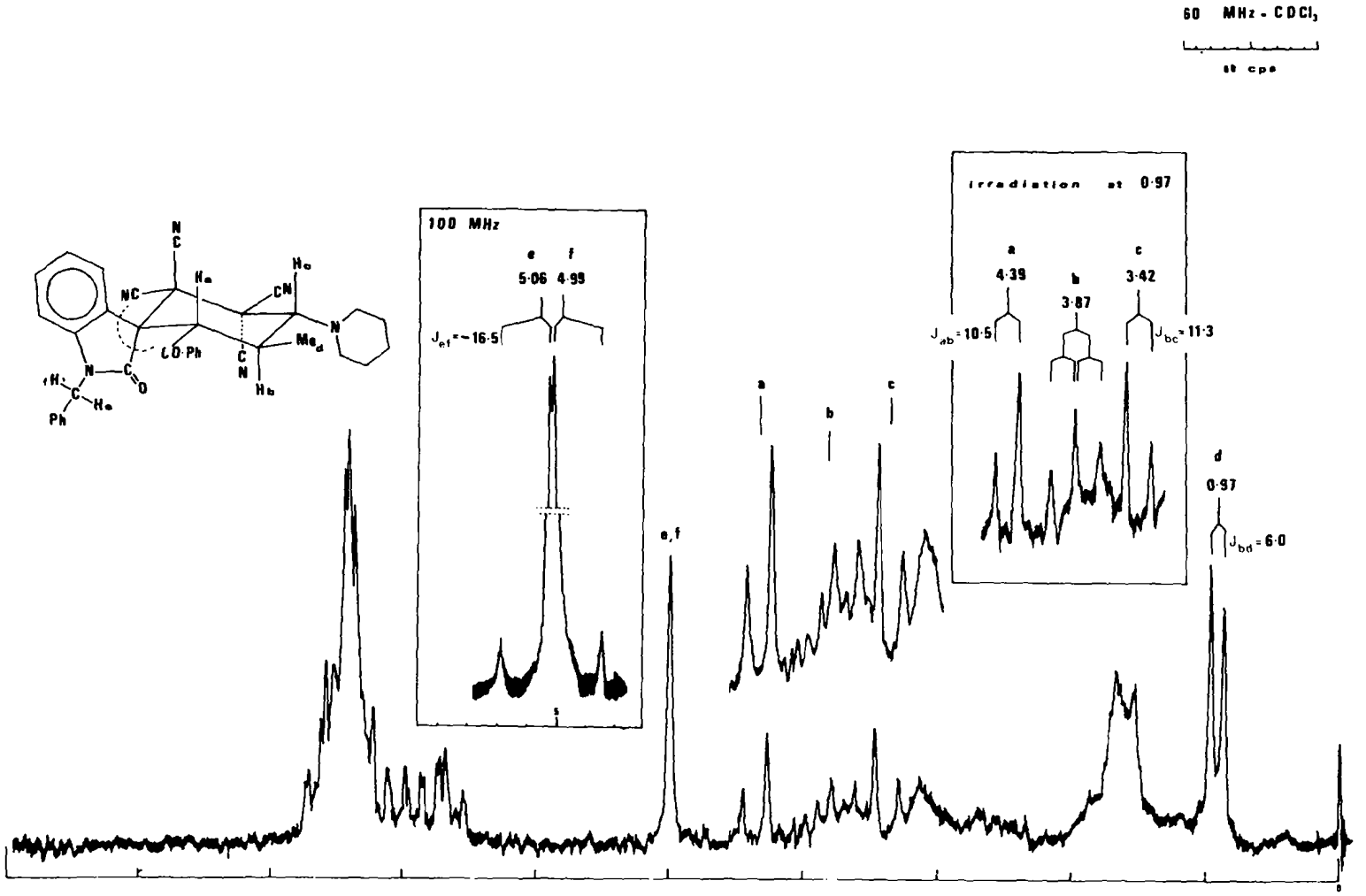


FIG 3. NMR spectrum of spiro[(2,2,3,3-tetracyano-4-piperidyl-5-methyl-6-benzoyl)cyclohexane-1,3'(1'-benzyl)oxindole] (IIIc) and its spin decoupling spectra run on a Perkin–Elmer R-12 A. In addition benzylic protons are registered on Varian A-100 spectrometer.

In this scheme, in addition to the decomposition of the cyclic adducts, we have also included their formation, although the mechanism seems here less reliable.

The formation of cyclobutanes or dihydropyrans from N-alkyl and N-acyl derivatives is well explained in terms of a net charge distribution, hence through a zwitterionic pathway.

In a few border cases (*e.g.* when R = H or $PhCH_2$), where the charge distribution of the diene is not well defined, the choice between the different reaction pathways must depend on the polar character of the dienophile double bond. The stronger nucleophilic 1-piperidino-1-propene leads through a zwitterion to the cyclobutane derivative, whereas the less nucleophilic 1-pyrrolidino-1-isobutene gives rise to the dihydropyran. In the latter case a concerted mechanism cannot be excluded.

Whatever the mechanism of formation may be, every cyclic adduct must be in equilibrium with its stabilized zwitterion, whose presence is substantiated by the reaction with TCE.

In chloroform the kinetically controlled reaction product is still the cyclic adduct but this, under thermodynamic conditions, is transformed through the zwitterion into the more stable Michael adducts. This latter compound therefore becomes the final product of the reaction between oxindolideneacetophenones and β-monomethyl substituted enamines.

We previously reported,[2] but did not interpret, the hydrolytic cleavage that dihydropyran and cyclobutane adducts undergo in dilute acetic acid. In this polar medium the formation of the same dipolar intermediate should be favoured.[10]

The zwitterion immediately undergoes a 1,4- or 1,6-addition of water, followed by elimination of the base residue and formation of the open-chain aldehyde. The alternative nucleophilic attack of water on the closed adducts, considering the present results, can be reasonably excluded.

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 Perkin–Elmer R 12 A spectrometer: microanalyses by Dr. Lucia Maggi Dacrema.

Thermal rearrangement of dihydropyrans and spiro-cyclobutanes

The spiro-cyclobutanes and dihydropyrans[2] (I) were dissolved at − 20° in $CDCl_3$ (conc 0·6 Mol) and the soln left until its temp, after about 1 hr, reached the temp of registration (+ 35°).

The adducts Ib, d, f, h were completely decomposed and their NMR spectra found identical with the spectra of the corresponding 3-oxindolideneacetophenones[2] and of 1-pyrrolidino-1-isobutene.

The adducts Ie, g show the spectra of the corresponding enamines IIe, g.

The adducts Ic and Ia have the spectra of the enamines IIc and IIa, without any trace of the starting spiro-cyclobutane, after 5 hr and 24 hr respectively.

Reaction of dihydropyrans and spiro-cyclobutanes with TCE

(I → III)

Method A. To a cooled and stirred suspension of TCE (0·128 g, 1 mmole) in chloroform (10·0 ml), Ia resp. Ib (1 mmole) was added. The clear orange soln was stirred and, after a few mins, light petroleum (24·0 ml) was added dropwise.

The white crystalline ppt was filtered off and washed with a small quantity of light petroleum. The crude adducts thus obtained included variable amounts of chloroform and were dried to constant weight: IIIa, 3 hr at 100°, 0·4 mm pressure: IIIb, 4 hr at 80°, 0·4 mm pressure. The dried adducts appear as yellow-green and brown crystals respectively.

TABLE 3

Compd	Method	Physical aspect (Yield %)	m.p.	Elementary analysis		I.R. Spectra			
						ν C≡N	ν C=O lactam	ν C=O acyl	ν C=O ketone
IIIa	A	yellow-green crystals (90–92)	119–121°	for $C_{31}H_{28}N_6O_2$	found: C, 72·23; H, 5·64; N, 15·92 calc: C, 72·07; H, 5·46; N. 16·27%	2195 m	1728 s	—	1677 s
	B	white needles (88–90)	130–131°	for $C_{31}H_{28}N_6O_2 + \frac{1}{2}$AcOEt	found: C, 71·00; H, 5·99; N, 15·15 calc: C, 70·69; H, 5·75; N, 14·99%	2248 w	1720 s	—	1680 s
		brown-green crystals	119–121°	for $C_{31}H_{28}N_6O_2$	found: C, 71·75; H, 5·51; N, 16·17 calc: C, 72·07; H, 5·46; N, 16·27%	2195 m	1728 s	—	1677 s
IIIb	A	brown crystals (68–70)	104–106	for $C_{31}H_{28}N_6O_2$	found C, 71·93; H, 5·51; N, 16·10 calc: C, 72·07; H, 5·46; N, 16·27%	2200 m	1740 s	—	1672 s
	B	yellow-green needles (85–86)	109–110°	for $C_{31}H_{28}N_6O_2 + \frac{1}{2}$AcOEt	found: C, 71·05; H, 5·75; N, 15·36 calc: C, 70·69; H, 5·75; N, 14·99%	2240 w	1735 s	—	1671 s
		brown crystals	104–106°	for $C_{31}H_{28}N_6O_2$	found: C, 71·83; H, 5·61; N, 16·00 calc: C, 72·07; H, 5·46; N, 16·27%	2200 m	1740 s	—	1672 s
IIIc	B	white needles (83–86)	135–136°	for $C_{37}H_{32}N_6O_2$	found: C, 74·72; H, 5·56; N, 13·91 calc: C, 74·98; H, 5·44; N, 14·18%	2242 w	1734 s	—	1680 s
IIId	B	cream needles (88–90)	110–111°	for $C_{37}H_{32}N_6O_2$	found: C, 74·60; H, 5·61; N, 13·82 calc: C, 74·98; H, 5·44; N, 14·18%	2242 w	1739 s	—	1675 s
IIIe	B	white needles (58–60)	115–117°	for $C_{32}H_{28}N_6O_3$	found: C, 70·67; H, 5·21; N, 15·45 calc: C, 70·57; H, 5·18; N, 15·43%	2247 w	1769 s	1731 s	1673 s
IIIg	B	white needles (71–73)	126–128°	for $C_{37}H_{30}N_6O_3$	found: C, 73·48; H, 5·00; N, 13·52 calc: C, 73·25; H, 4·98; N, 13·85%	2248 w	1751 s	1703 s	1665 s
IIIh	B	yellow-green needles (58–60)	130–132°	for $C_{37}H_{30}N_6O_3$	found: C, 72·88; H, 5·02; N, 13·57 calc: C, 73·25; H, 4·98; N, 13·85%	2240 w	1754 s	1692 s	1669 s

Method B. To a stirred soln of TCE (0·128 g, 1 mmole) in AcOEt (4·0 ml), Ia, b, c, d, e, f, g, h (1 mmole) was added rapidly and after a few mins from the clear solution a white crystalline product precipitated. The solid was filtered off and washed with a little AcOEt. For Ie, the crystalline adducts began to precipitate after 20 mins and was filtered after 1 hr. For If, attempts to isolate the crystalline adduct were unsuccessful. IIIb, d, h after filtration may be kept white at low temp and in the dark; but room and light rapidly cause a yellow greenish colour.

Attempts to crystallize the adducts (III) led to unsatisfactory results; some solvents (EtOH, diisopropyl ether) cause decomposition, others give crystalline products including variable amounts of solvent. Correct values for elementary analysis of all adducts were obtained from crude samples dried for 8 hr at room temp and 0·4 mm pressure. IIIa and IIIb include ½ mole of AcOEt and were dried up to a constant weight (IIIa: 2 hr, 100°, 0·4 mm pressure; IIIb: 4 hr, 80°, 0·4 mm pressure).

Yields, physical aspect, elementary analysis and IR spectra of all the isolated adducts are summarized in Table 3.

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