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# HETERODIENE SYNTHESES—XXIV[1]

## CHANGES IN THE REACTIVITY OF 2-OXOINDOLIN-3-YLIDENE DERIVATIVES WITH ETHYLVINYLETHER INDUCED BY ELECTRON-WITHDRAWING GROUPS. THE IMPORTANCE OF THE LUMO COEFFICIENTS

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**Abstract**—Ethylvinylether reacts in acetonitrile with 1 - acetyl - 2 - oxoindolin - 3 - ylidene derivatives $\beta,\beta$ - disubstituted with electron-withdrawing substituents. When the $\beta$-substituents act by inductive effect alone, a regiospecific $\beta$-attack† occurred giving rise, through a 1,4 - cycloaddition, to 2,3 - dihydropyran[2,3-b]indoles. As a by product Michael adduct can be obtained. When the $\beta$-substituent act by conjugative effect also, a regiospecific $\alpha$-attack† occurred giving rise to spiro - dihydropyrane or - cyclobutane - 2 - oxoindolines depending on the nature of the substituents.

In a less polar solvent, the latter ones are formed together with the adduct arising from the regioisomeric $\beta$-attack.

The overall reactivity can be rationalized in terms of LUMO coefficients of the heterodiene and of different stabilization offered by the solvent to the various reaction pathways.

It is known that heterodiene syntheses can take place by different pathways: 1,4- and 1,2 - cycloaddition,[2] Michael reactions[3] and stable zwitterions[1] also (Scheme 1 A–D) when enamines and aminals are allowed to react with 2 - oxoindolin - 3 - ylidene derivatives.

The lower the orbital separation between the HOMO of the olefin and the LUMO of the $\alpha,\beta$-unsaturated carbonyl derivative, the higher is the electron transfer from the donor to the acceptor and hence the stronger is the zwitterionic character of the reaction.[4]

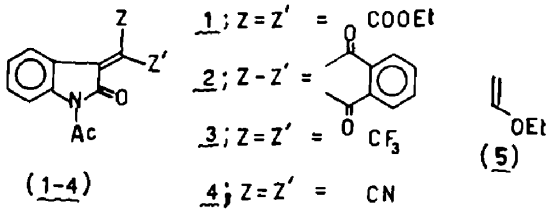
Similar behaviour was found in the reaction of 2 - oxoindolin - 3 - ylidene derivatives with ethylvinylether. The higher frontier MO separation involved in 3 - benzylidene compounds gives rise to 1,4 - cycloadditions only.[5] When the oxoindolin LUMO is lowered by an electron withdrawing substituent in the 3 - ylidene position, 3 - (2 - oxoindolin - 3 - yl)dihydrofurans are obtained as by-products, via a zwitterionic intermediate[6] (Scheme 1 E). Even if the regioselectivity of the reaction could have changed depending on the amplitude of the reagent coefficients, a $\beta$ attack (Scheme 1) was always observed.

Simple considerations of the effect of substituents, suggest that two strong electron withdrawing groups in the $\beta$ position could lower the heterodiene LUMO enough to direct the reactivity to a zwitterionic pathway with vinylethers also, and could increase the $\alpha$ coefficient enough to overwhelm the $\beta$ one changing the regioselectivity of the attack.

In addition to the amplitude of the LUMO coefficients and the eventual steric effects, further points had to be taken into account in the balance between $\alpha$ and $\beta$ attack: (i) the aromaticity which can be gained by an adiacent ring when a $\beta$ attack occurs; (ii) the "allowance"[7] of a reaction which can lower its energy of activation.

†Throughout the text, and $\alpha$ and $\beta$ positions refer to the unsaturated carbonyl system including the lactam carbonyl.

To investigate the effect of two $\beta$-electron withdrawing substituents on both the nature of the t.s. and the regioselectivity, we have performed the reaction between 1 - acetyl - 2 - oxoindolin - 3 - ylidene $\beta,\beta$ - disubstituted derivatives (**1–4**) and ethylvinylether (**5**).




### RESULTS AND DISCUSSION

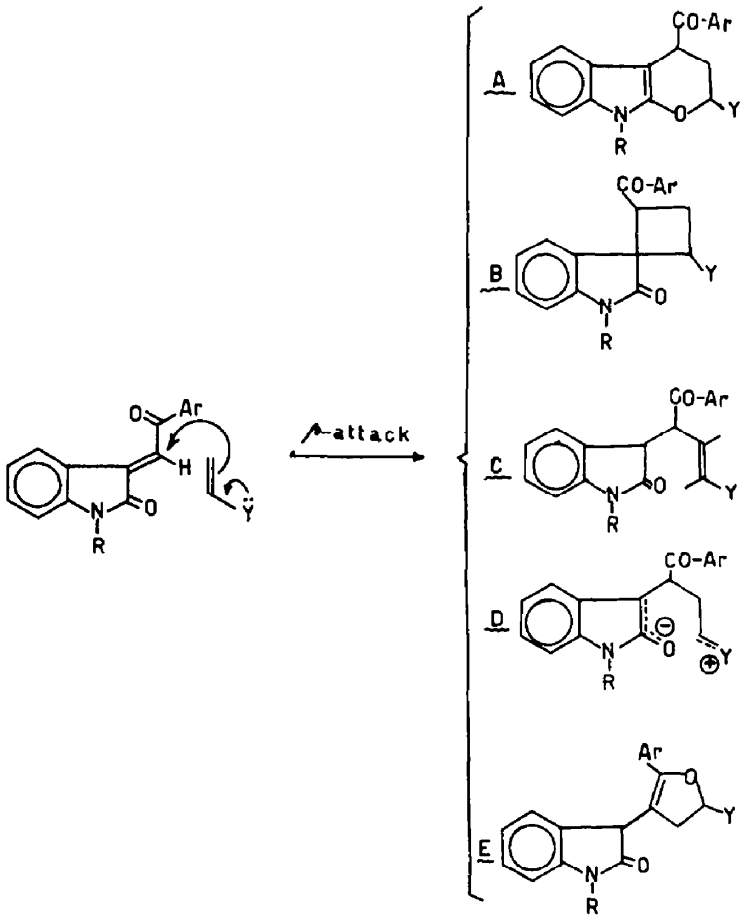
All reactions were initially performed at room temperature in acetonitrile, a solvent whose high dielectric constant would offer better stabilization to any developing zwitterion.

(a) *Reaction with* 1 - *acetyl* - 2 - *oxoindolin* - 3 - *ylidene diethylmalonate* (**1**)

After about 2 weeks a single colorless adduct (**6**) was obtained (reaction a Scheme 2) in a quantitative yield. The structure of 2 - ethoxy - 4,4 - dicarbethoxy - 9 - acetyl - 2,3 - dihydropyran[2,3 - b]indole was assigned on the basis of the IR spectrum (Experimental) and of the chemical shift of the anomeric $H_a$ proton whose value at 5.52$\delta$ is consistent with an acetal-type proton.

(b) *Reaction with* 2 - (1 - *acetyl* - 2 - *oxoindolin* - 3 - *ylidene*)1,3 - *indandione* (**2**)

After 3 days a quantitative yield of a yellow mixture of diastereomeric adducts (**7a,b**) was obtained (reaction b Scheme 2). The IR spectra show lactam, acetyl and ketone carbonyls and a dihydropyran type double bond. The NMR spectra have the X part of an ABX pattern resonating at 5.88 (**7a**) and 5.76 (**7b**) $\delta$, consistent with




Scheme 1.

acetal type protons. These data suggest that **2** reacted in accordance with a 1,4 - cycloaddition, but involving the indane fragment instead of the heterocyclic one. Hence the spiro[2,3,4,5 - tetrahydro - 2 - ethoxy - 5 - ketoindano[1,2 - b]pyran - 4 - 3'(1' - acetyl - 2' - oxo)indoline] structure was assigned to **7**.

Several factors could account for the different regioselectivity of **2** in addition to the $\alpha$ coefficient being greater than the $\beta$ one because of the effect of two largely coplanar CO groups. A new [4 + 2] allowed cycloaddition possibility; the indenone conjugation developed in **7** which can partly counterbalance the ungained indole aromaticity; the severe hindrance to the approach to the heterocyclic C=C–C=O fragment given by the Z-carbonyl and the favourable entropy factor due to the rigid *cisoid* conformation of the *second* C=C–C=O system can be involved.

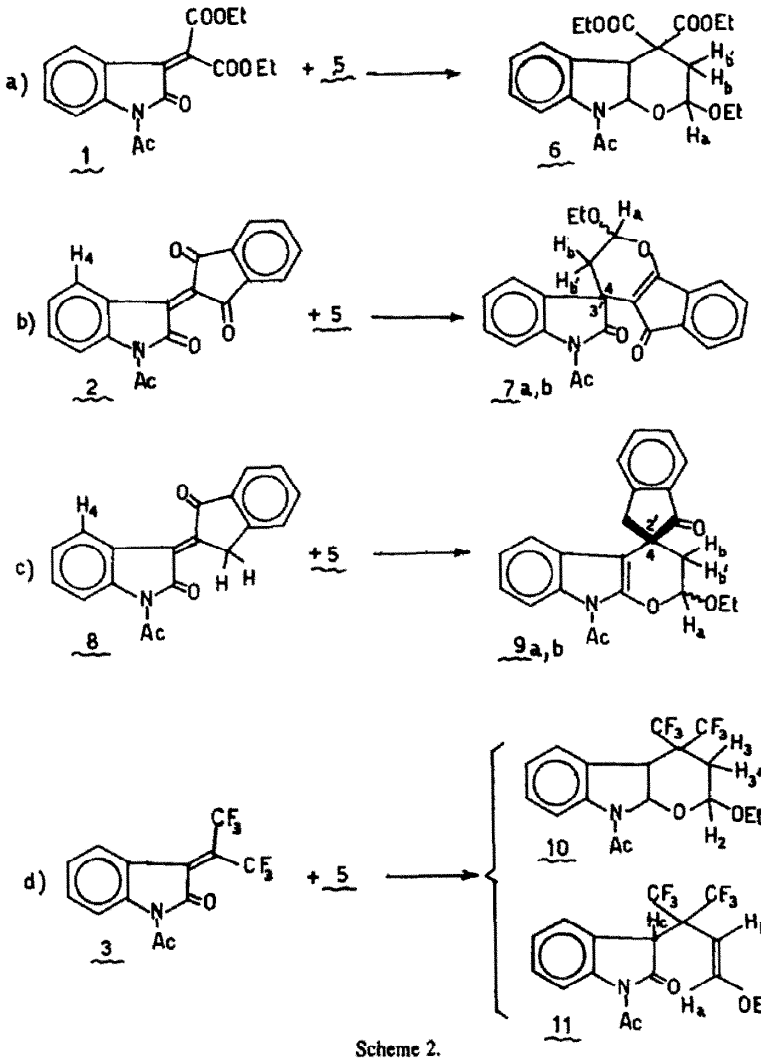
(c) *Reaction with* (*E*) 2 - (1 - *acetyl* - 2 - *oxoindolin* - 3 - *ylidene*) - 1 - *indanone* (**8**)

Some of the above mentioned factors were ruled out in the light of the reactivity of (E) - 2 - (1 - acetyl - 2 - oxoindolin - 3 - ylidene) - 1 - indane (**8**) with **5**. Even if the experimental condition (vinylether excess at 100° in a Paar bomb, conditions which will be tested later for all substrates) are somewhat different due to the low reactivity of **8**, since a diastereomeric mixture of spiro (2 - ethoxy - 9 - acetyl) - 2,3 - dihydropyran[2,3 - b]indole - 4,2' - indan - 1' - one (**9a,b**) was obtained (reaction c, Scheme 2), the possibility of a second [4 + 2] cycloaddition and the favourable entropy factor are irrelevant to the regioisomeric change from **2** to **1**. Similarly the hindrance to the approach of **5** to the heterocyclic C=C–C=O system and to a certain extent the indenone conjugation seem insignificant since comparable factors can be found in **8**. Therefore, the regioselectivity of attack must be affected by the amplitude of the $\alpha$ coefficient being greater than the $\beta$ one. Certainly the effect of the electron withdrawing carbonyl groups must be greater in **2** than in **1**: we will come back later to the reason of this.

(d) *Reaction with* 2 - (1 - *acetyl* - 2 - *oxoindolin* - 3 - *ylidene*)*hexafluoropropane* (**3**)

The reaction occurs quickly (about 12 hr) and two products are separated by fractional crystallization and column chromatography. The structure of 2 - ethoxy - 4,4 - *bis*trifluoromethyl - 9 - acetyl - 2,3 - dihydropyran[2,3 - b]indole was assigned to the high yield isomer **10** on the basis of IR and NMR data (Experimental). The low yield isomer **11** (reaction d, Scheme 2) has a lactam carbonyl at 1765 $cm^{-1}$ and a vinylether type double bond at 1670 $cm^{-1}$. The NMR spectrum shows two coupled olefinic protons at 6.45 and 4.41$\delta$ respectively (J = 7.5 Hz) and a singlet (1 H) at 5.21$\delta$. This, and the high field olefinic proton are long range coupled ($\leq$1 Hz) with fluorine. On the basis of these the structure of 3 -(1' - ethoxy - 3',3' - *bis*trifluoromethyl - 3' - propenyl) - 1 - acetyl - 2 - oxoindoline was assigned.

The regioisomeric structure of **11** arising from attack in the $\alpha$ position was ruled out since it would lead to a



Scheme 2.

$-CH(CF_3)_2$ group with a proton having a coupling constant with fluorine much larger than that detected in **11**. These results reflect a tendency towards both a zwitterion pathway (**11** comes from this mechanism only) and a high $\beta$ - regioselectivity of attack.

This dicotomy can be rationalized if we consider that electron withdrawing substituents (Z) can simply act through the inductive effect (Zi such as $CF_3$ or non planar CO groups†) or also by conjugation (Zc coplanar carbonyls of the indandione derivative **2**).

If we take the acrolein LUMO as a model (Fig. 1), the coefficient is larger than the $\alpha$ one.[8]

Simple considerations of substituent effects suggest that Zi substituents decrease the LUMO energy and, lowering the larger coefficient ($\beta$) and raising the smaller ($\alpha$), make the $\alpha$ and $\beta$ coefficients comparable.

Since it is well known that simple conjugation lowers the LUMO and decreases the coefficient at the C atom carrying the conjugating group, Zc substituents markedly lower the LUMO and make the $\alpha$ coefficient larger than the $\beta$ one because of the sum of inductive and conjugative effects.

†The overcrowdness of the $\beta$ position of **1** should cause a strong twisting out of conjugation of -COOEt groups with the oxindolin - 3 - ylidene fragment.

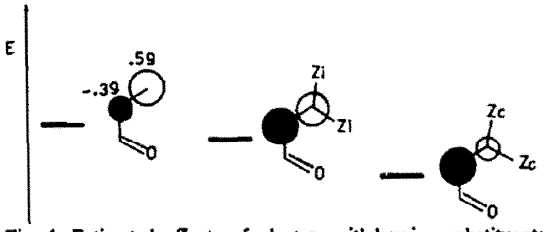


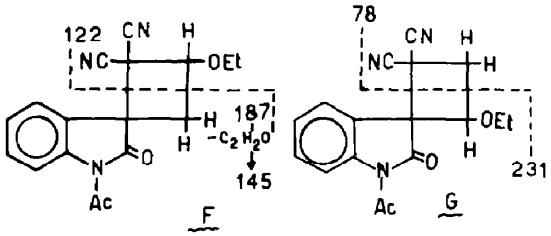

Fig. 1. Estimated effects of electron-withdrawing substituents (e.w.s.) (Zi = e.w.s. acting by inductive effect only; Zc = e.w.s. acting by resonance also) on LUMO energy and coefficients of acrolein.

Hence Zi substituents are eventually expected to act as "zwitterion-promoters" through a $\beta$ attack. The Zc substituents should act as "$\alpha$ attack promoters" giving rise, if no other allowed reaction is possible, to a zwitterionic pathway. That is what is expected for the following reaction.

(e) *Reaction with* 1 - *acetyl* - 2 - *oxoindolin* - 3 - *ylidenemalononitrile* (**4**)

The reaction occurs within a few days and two colourless adducts **12** and **13**, with a total yield of about 95%, were isolated. Both isomers have an IR spectra showing the lactamic carbonyl at about 1760 $cm^{-1}$. The NMR

excludes a Michael addition for both since no AX system of olefinic protons occur; both have ABX systems whose chemical shifts are consistent with cyclobutanic structures arising from [1,2] cycloaddition on the exocyclic double bond.




Two regioisomeric structures are possible (**F** and **G**), each having two diastereomeric possibilities.

It is known that cyclobutane derivatives undergo cycloreversion to two olefins under the conditions for mass fragmentation[9] and also under thermal conditions,[10,11] especially when the high energy of activation required for a 2s + 2a mechanism is lowered by stabilized intermediates.[12]

Since the mass spectra of both adducts gave a fragment at *m/e* 122 consistent with 1,1 - dicyano - 2 - ethoxyethene and two ions at *m/e* 187 and 145 consistent with 3 - methylene - 2 - oxoindoline, both **12** and **13** are (**F**) diastereoisomers.

To confirm this assumption the thermal cycloreversion was performed under conditions allowing 3 - methylene - 2 - oxoindoline eventually formed to be trapped. Therefore both **12** and **13** were heated at 100° in a Paar bomb in the presence of **5** for about 2 days. Column chromatography of the reaction mixture gave good yields of 1,1 - dicyano - 2 - ethoxyethene[13] (**14**) and 2 - ethoxy - 9 - acetyl - 2,3 - dihydropyran[2,3 - b]indole (**16**) clearly obtained by a heterodiene synthesis on the second fragment: 1 - acetyl - 3 - methylene - 2 - oxindoline (**15**) (Scheme 3).

These results confirm that both **12** and **13** are the diastereoisomers spiro[(2,2 - dicyano - 3 - ethoxy)cyclobutan - 1,3' - (1' - acetyl) - 2' - oxoindoline] with the high yield isomer **12** being the one with the lactam carbonyl and the ethoxy group in a *trans* relationship as suggested by the shift of the NMR signals of the cyclobutane protons.

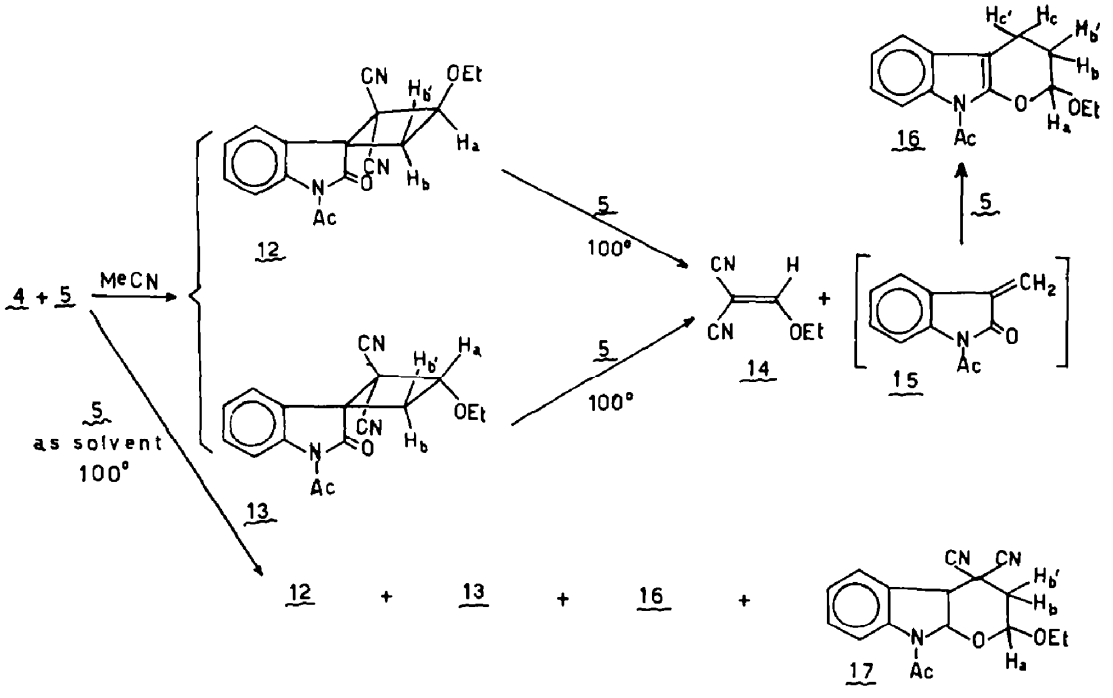
The regiospecific $\alpha$-attack to give cyclobutanes is expected on the basis of previous considerations of the effect of Zc substituents and can be attributed to the development of the greater LUMO coefficient in $\alpha$. Since the $\alpha$-attack gives rise to a zwitterion which is the intermediate along the reaction coordinate, a significant contribution to this choice could be offered by the solvent which acts by lowering the energy of activation of the reaction by solvation of the dipolar intermediate. To test this we investigate the reaction of **1-4** with **5** under conditions consistent with a reasonable rate, but in the presence of a solvent of low dielectric constant to minimize stabilization of the developing zwitterion. Ethylvinylether was used in excess as solvent at 100° in a Paar bomb.

(f) *Reactions of* **1-4** *in ethylvinylether as solvent*

The reactivity of **1**, **2** and **3** do not change significantly meaning that [4 + 2] cycloadditions are rather insensitive to the solvent.

A much different result occurs with **4** since a third adduct is isolated in addition to **12** and **13** obtained previously. This new colourless compound (**17**), which from the spectral characters (Experimental) is 2 - ethoxy - 4,4 - dicyano - 9 - acetyl - 2,3 - dihydropyran[2,3 - b]indole, is a primary reaction product since it is stable and neither **12** nor **13** are transformed into **17** under the reaction conditions (Scheme 3).

Rationalization of this result can be found in terms of loss of solvation energy for the zwitterion which is the intermediate in the formation of **12** and **13**. The resulting increase in the energy of activation for this reaction




Scheme 3.

makes the $\beta$-attack, whose [4+2] cycloaddition is less sensitive to the solvent polarity, comparable.

## CONCLUSION

Several examples of regioisomeric variation are known in the field of cycloaddition. Well studied examples of 1,3 - dipolar cycloadditions[4,14,15] and Diels–Alder reactions[16,17] were rationalized from frontier orbital theory considering the overlap between the greater coefficients in the dominant HOMO/LUMO interaction.

From this point of view the factors determining the regioisomerism of the above reported adducts are not new. The novelty is that these factors do not only give different regioisomers of the same ring, but different reaction modes giving rise to [4+2] or [2+2] or Michael adducts.

A further point needs to be considered concerning the different behaviour of **4** in acetonitrile and vinylether. In the polar solvent $K_{[2+2]} \gg K_{[4+2]}$ since no dihydropyran is formed. In the less polar solvent $K_{[2+2]} \simeq K_{[4+2]}$ since comparable amounts of cyclobutanes and dihydropyranes are obtained.

In the light of the solvent theory of Hughes and Ingold[18] which can be applied to cycloadditions with polar intermediates,[19] this can be interpreted as evidence for a two-step mechanism in the formation of cyclobutanes and for a largely concerted pathway to dihydropyrane derivatives.

The [4+2] cycloadditions, coming from either a $\beta$ attack on **1**, **3**, **4** or from an $\alpha$ attack on **2**, occur through a t.s. where the synchronous hybrid can counterbalance the stabilization which is lost by the zwitterionic one when the solvation energy is lacking.

## EXPERIMENTAL

All m.ps are uncorrected. IR spectra (Nujol mulls) were determined on a Perkin–Elmer 257 spectrophotometer. NMR spectra were obtained in $CDCl_3$ on a Perkin–Elmer spectrophotometer (chemical shifts are reported in ppm on the $\delta$ scale, coupling constants in Hz). Mass spectra were obtained on a Du-Pont 21-492 B mass spectrometer via the direct probe and vaporized at temperatures between 50 and 80°. Microanalyses were performed by Dr. Lucia Maggi Dacrema.

*1 - Acetyl - 2 - oxoindolin - 3 - ylidene derivatives* (**1–4, 8**)

*1 - Acetyl - 2 - oxoindolin - 3 - ylidene diethylmalonate* (**1**). Obtained from 2 - oxoindolin - 3 - ylidene diethylmalonate[20] by acetylation following the lit,[21] as yellow prisms (Table 1).

*2 - (1 - Acetyl - 2 - oxoindolin - 3 - ylidene)1,3 - indandione* (**2**). From 1 - acetylisatin (0.01 mol) and 1,3 - indandione (0.01 mol) in EtOH (15 ml) and $Et_3N$ (few drops) following the lit.[23] 2 - (1 - Acetyl - 2 - oxo - 3 - hydroxy - 3 - indolinil) - 1,3 - indandione was obtained (87%); m.p. 135° (benzene) (Found: C, 68.32; H, 3.91; N, 4.25. Calc. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18%). The isolated product was suspended in $SOCl_2$ (20 ml) and refluxed until no gas evolution was observed (about 2 hr). The red soln was evaporated to dryness and the residue was ground with diethyl ether, thus obtaining **2** as red-violet prisms (Table 1).

*2 - (1 - Acetyl - 2 - oxoindolin - 3 - ylidene)hexafluoropropane* (**3**). An excess of exafluoroacetone sesquihydrate (2 ml) was slowly dripped into conc $H_2SO_4$ (7 ml) under vigorous stirring, and anhyd. exafluoroacetone was bubbled into a well stirred soln of oxindole (1.4 g, 0.01 mole) in 30 ml of anhyd pyridine. After stirring overnight, the reddish soln was evaporated, and the residue was ground with light petroleum and filtered off. 2 - (2 - Oxo - 3 - indolin) - 2 - hydroxyhexafluoropropane was obtained (2.5 g, 85%) white-pinky needles m.p. 177–178° (benzene). (Found: C, 44.34; H, 2.38; N, 4.76. Calc for $C_{11}H_7F_6NO_2$: C, 44.15; H, 2.34; N, 4.68%.) The isolated product was suspended in $PCl_3$ (30 ml) and gently refluxed until no gas evolution was observed (5–6 hr). After cooling on an ice bath, red crystalline solid separated which was filtered off and washed with water. 2 - (2 - Oxoindolin - 3 - ylidene)hexafluoropropane was obtained in nearly quantitative yield as orange needles, m.p. 128–129° (EtOH dil). (Found: C, 47.10; H, 1.94; N, 5.03. Calc. for $C_{11}H_5F_6NO$: C, 46.98; H, 1.88; N, 4.98%.) By acetylation following the lit[21] **3** was obtained as soft yellow needles (Table 1).

*1 - Acetyl - 2 - oxoindolin - 3 - ylidenemalononitrile* (**4**). A suspension of 1 - acetylisatin (0.01 mol), malononitrile (0.01 mol) in benzene (60 ml) and piperidine (few drops) was stirred at room temp. After 45 min the red soln was evaporated and the residue was ground with diethyl ether and filtered off. **4** was obtained as red-orange needles (Table 1).

*(E) 2 - (1 - Acetyl - 2 - oxoindolin - 3 - ylidene) - 1 - indanone* (**8**). Following the lit,[23] by condensation of equimolecular amounts of isatin and 1 - indanone, and dehydration of the aldolic intermediate. Deac **8** was obtained (73%) as red needles m.p. 250° dec. (dioxane); (Found: C, 74.07; H, 4.13; N, 5.41. Calc. for $C_{17}H_{11}NO_2$: C, 74.32; H, 4.21; N, 5.36%). A mixture of $Ac_2O$ (10 ml) and a few drops of conc $H_2SO_4$ was added with 1.05 g (4 mmole) of the 1 - unsubstituted derivative, and refluxed 5 min. The soln was cooled and yellow needles of **8** were filtered off and washed with diethyl ether, $NaHCO_3$ (5% soln) and water. The (E) configuration was assigned on the basis of the $H_4$ NMR signal resonating at 9.30$\delta$, as compared with $H_4$ signal of **2** at 9.10$\delta$ (Scheme 2). Table 1 summarized the characteristics of the above mentioned compounds **1–4, 8**.

*Reaction of* **1** *with* **5**.

(a) A mixture of **1** (4 mmole) and **5** (40 mmole) in MeCN (10 ml) was kept at room temp for about 2 weeks, and then evaporated to dryness, yielding **6** in a quantitative yield as white needles, m.p. 84–85° (EtOH); $\nu_{max}$($CHCl_3$): 1735 broad, 1712, 1631 $cm^{-1}$ (ester, acetyl and C=C dihydropyran respectively); NMR $\delta$ 5.22 (1 H, dd, $H_a$, $J_{ab} + J_{ab'} = 8.4$), 2.8 (1 H, dd, $H_b$), 2.59 (1 H, dd, $H_{b'}$). (Found: C, 62.41; H, 6.37; N, 3.61. Calc. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47%.)

(b) A suspension of **1** (4 mmol) and **5** (12 ml) was heated at 100° in a Paar bomb for 5 hr giving **6** in nearly quantitative yield.

*Reaction of* **2** *with* **5**

Starting from **2** and following the previously described method (a), after 3 days a quantitative yield of the diastereomeric mixture of **7a** and **7b** was obtained in 60/40 ratio (based on the NMR acetyl signals). Pure isomers were obtained by fractional crystallization (**7a** from EtOH; **7b** from toluene) or by column chromatography (Kieselgel Merk H, $CH_2Cl_2$ as eluant). **7a**: Yellow needles, m.p. 175–176° (EtOH); IR: 1763, 1708, 1638 $cm^{-1}$ (C=O lactam, C=O acetyl and ketone and C=C dihydropyran respectively). NMR 5.88 (1 H, dd, Ha; $J_{ab} + J_{ab'} = 8.6$), 2.15–2.55 (2 H, m, $H_b$ and $H_{b'}$; for $H_a$, $H_b$, $H_{b'}$ see formulae in Scheme 2). (Found: C, 70.61; H, 4.94; N, 3.63. Calc. for $C_{23}H_{19}NO_5$: C, 70.94. H, 4.92; N, 3.60%). **7b**; yellow prisms, m.p. 193–194° (toluene); IR: 1750, 1700, 1632 (C=O lactam, C=O acetyl and ketone, C=C dihydropyran respectively). NMR: 5.76 (1 H, dd, $H_a$; $J_{ab} + J_{ab'} = 12.6$), 2.52 (1 H, dd, $H_b$), 2.09 (1 H, dd, $H_{b'}$). (Found: C, 70.68; H, 4.83; N, 3.65. Calc. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60%.)

Following the method (b), after 2 hr a quantitative yield of the mixture of **7a** and **7b** was obtained in a 55/45 ratio.

*Reaction of* **3** *with* **5**

Starting from **3**, following the method (a) the solid residue (12 hr) was ground with light petroleum and filtered off. Pure **10** (1.32 g, 83%); white prisms, m.p. 132–133° ($CH_3CN$); IR: 1725, 1620 (C=O acetyl and C=C dihydropyran). NMR: 5.49 (1 H, dd, $H_2$; $J_{2,3} + J_{2,3'} = 12$) 2.3–2.6 (2 H, m, $H_3$ and $H_{3'}$) (for $H_2$, $H_3$, $H_{3'}$ see formulae Scheme 2). (Found: C, 51.38; H, 3.58; N, 3.72. Calc. for $C_{17}H_{15}F_6NO_3$: C, 51.65; H, 3.80; N, 3.54%.) The mother liquor were columnchromatographed (Kieselgel H Merck, toluene as eluant) obtaining first a further 5% of **10**, followed by **11** (9%) as white prisms, m.p. 95–96° (light petroleum); (Found: C, 51.42; H, 3.88; N, 3.60. Calc. for $C_{17}H_{15}F_6NO_3$: C, 51.65; H, 3.80; N, 3.54%.)

Following the method (b), after 1 hr, **10** and **11** were obtained in a 9/1 ratio.

Table I.

| Compd | Yield % | m.p. (solvent) | Elementary analisis | IR $cm^{-1}$ νC=O lactam | νC=O ester | νC=O acetyl | νC=O ketone |
|---|---|---|---|---|---|---|---|
| 1 | 70 | 145-146 (EtOH) | found: C,61.93; H,5.28; N,4.31<br>for $C_{17}H_{17}NO_6$ calc : C,61.63; H,5.17; N,4.23% | 1760 | 1730[a] | | ---- |
| 2 | 85 | 190 (toluene) | found: C,71.80; H,3.61; N,4.24<br>for $C_{19}H_{11}NO_4$ calc ; C,71.92; H,3.49; N,4.41% | 1760 | ---- | 1715 | 1692[b]<br>1728 |
| 3 | 87 | 70-71 ($H_2O$/EtOH) | found: C,48.50; H,2.19; N,4.33<br>for $C_{13}H_7F_6NO_2$ calc : C,48.30; H,2.17; N,4.33% | 1766 | ---- | 1721 | ---- |
| 4 | 85 | 178-179 (toluene) | found: C,65.60; H,3.21; N,17.68<br>for $C_{13}H_7N_3O_2$ calc : C,65.82; H,2.97; N,17.72% | 1765 | ---- | 1718 | ---- |
| 8 | 70 | 181-182 (EtOH) | found: C,74.96; H,4.31; N,4.84<br>for $C_{19}H_{13}NO_3$ calc : C,75.24; H,4.32; N,4.62% | 1742 | ---- | 1726 | 1695 |

[a] broad band. [b] See reference (22).

*Reaction of* **4** *with* **5**

Starting from **4** (method a), after 6 days the white solid separated from the soln was collected and washed with diethyl ether. Pure **12** (47%) was obtained as white platelets, m.p. 158–159° (diisopropyl ether); IR: 1760, 1714 (C=O lactam and C=O acetyl). NMR: 5.03 (1 H, t, $H_a$; $J_{a,b}+J_{a,b'}=17.3$), 2.7–3.1 (2 H, m, $H_b$ and $H_{b'}$); *m/e*: 309 ($M^+$, <1) 187 (15), 145 (100), 122 (11), 117 (57), 72 (19). (Found: C, 65.95; H, 4.92; N, 13.50. Calc. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59%.)The mother liquors were evaporated and the residue was ground with diethyl ether and filtered off yielding a mixture of **12** and **13** (48%) in the 80/20 ratio (based on the $H_a$ NMR signals in $C_6D_6$ soln). Column graphic separation, during which some decomposition of **12** and **13** occurred (Kieselgel 0.06–0.2; ciclohexane–AcOEt 80/20 as eluant) gave first a further crop of **12** followed by (1SR,3SR) - spiro[(2,2 - dicyano - 3 - ethoxy)cyclobutan - 1,3' - (1' - acetyl) - 2' - oxoindoline] (**13**), white platelets, m.p. 151–152° (EtOH); IR: 1763, 1710 (C=O lactam and acetyl respectively). NMR: 4.87 (1 H, dd, $H_a$, $J_{ab}+J_{ab'}=17.3$), 3.18 (1 H, dd, $H_b$), 2.73 (1 H, dd, $H_{b'}$); mass spectrum very similar to that of **12**, with *m/e*: 309 ($M^+$, <1), 187 (15), 122 (10). (Found: C, 66.21; H, 4.97; N, 13.72. Calc. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59%.) Eu (DPM)$_3$ experiments in $CDCl_3$ ($\rho=0.03$) showed a $\Delta\delta H_a=0.75$ for **12** and a $\Delta\delta H_a=0.48$ for **13**.

Following method (b) (16 hr), the oily residue after evaporation was treated with diethyl ether, and nearly pure **12** (18%) was collected. After standing and cooling of the mother liquors pure or nearly pure **17** was collected (20%), white prisms, m.p. 146–147° (EtOH). IR: 1720, 1625 (C=O acetyl and C=C dihydropyran). NMR: 5.61 (1 H, dd, $H_a$; $J_{ab}+J_{ab'}=6$), 2.38 (1 H, dd, $H_b$), 2.63 (1 H, dd, $H_{b'}$). (Found: C, 66.24; H, 4.99; N, 13.51. Calc. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59%.) Sometimes crystalline mixtures of **12** and **17** were also obtained. Ethereal mother liquors were evaporated and the oily residue was column chromatographed (Kieselgel 0.06–0.2 Merck; cyclohexane–AcOEt 80/20 as eluant). From the first fraction **16** was obtained (7%), pale yellow prisms, m.p. 82–83° (light petroleum). IR: 1700, 1640 (C=O acetyl and C=C dihydropyran). NMR: 5.43 (1 H, t, $H_a$, $J_{ab}+J_{ab'}=6.3$), 2.5–2.8 (2 H, m, $H_b$ and $H_{b'}$), 1.9–2.3 (2 H, m, $H_c$ and $H_{c'}$). (Found: C, 69.37; H, 6.60; N, 5.64. Calc. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61, N, 5.40%.) The second fraction gave a further crop of **12** (32–35% total yield), while only traces of **13** and of 1,1 - dicyanoethoxyethene **14** were recovered in the next fractions. Finally a further amount of **17** was obtained (31% total yield).

*Reaction of* **8** *with* **5**

A suspension of **8** (4 mmole) and **5** (10 mL) was heated at 100° in a Paar bomb for 5 days. After cooling and scratching of the concentrated soln, **9a** was collected, white prisms, m.p. 198–199° (EtOH). IR: 1712, 1708, 1635 (C=O acetyl, C=O ketone and C=C dihydropyran respectively). NMR: 5.41 (1 H, dd, $H_a$; $J_{ab}+J_{ab'}=12$); 2.47 (1 H, dd, $H_b$); 1.97 (1 H, dd, $H_{b'}$). (Found: C, 73.51; H, 5.69; N, 3.69. Calc. for $C_{22}H_{21}NO_4$: C, 73.60; H, 5.58; N, 3.72%). The mother liquors were evaporated and the reddish oily residue was column chromatographed (Kieselgel 0.06–0.2 Merck; cyclohexane–AcOEt 85/15 as eluant) and **9b** was obtained (8%), white prisms, m.p. 210° dec. (EtOH). IR: 1708, 1632 (acetyl and ketone C=O, C=C dihydropyran). NMR: 5.80 (1 H, dd, $H_a$; $J_{ab}+J_{ab'}=5.8$), 2.35 (1 H, dd, $H_b$), 2.15 (1 H, dd, $H_{b'}$). (Found: C, 73.83; H, 5.41; N, 3.89. Calc. for $C_{22}H_{21}NO_4$: C, 73.60; H, 5.58; N, 3.72%.) A second crop of **9a** (overall yield 54%) was obtained in the next fraction.

*Reaction of* **12** *and* **13** *with* **5** *at* 100°

A suspension of **12** (0.33 mmole) and **5** (2 ml) was heated into a sealed tube at 100° for 40 hr. The soln was evaporated, and the oily residue was column chromatographed (Kieselgel 0.06–0.2 Merck; cyclohexane/AcOEt 70/30 as eluant). From the first fraction **16** was obtained as a white-yellow solid (63%); from the second fraction **14** was recovered (50%), identified with an authentic sample, prepared by the reported method.[24]

Very similar results were obtained when **13** was allowed to react with **5** in the same conditions.

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