THE REACTION OF ISATIN AZOMETHINE YLIDES WITH (*Z*)- AND (*E*)-2-OXOINDOLIN-3-YLIDENE ACETOPHENONES: CONCERTED *VS* APPARENT NON-CONCERTED 1,3-DIPOLAR CYCLOADDITION#

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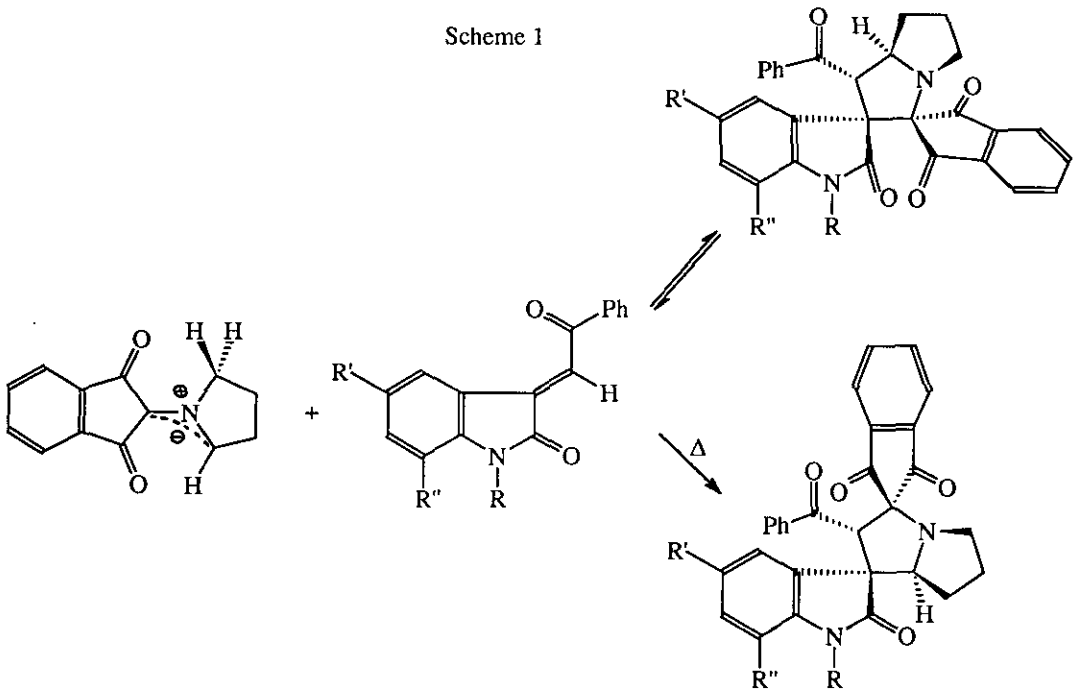
Abstract - The reaction of 1-benzyl-5-bromoisatin with proline, sarcosine, or glycine gives azomethine ylides that can be trapped by (*Z*)- or (*E*)-2-oxoindolin-3-ylidene acetophenones acting as dipolarophiles in a 1,3-dipolar cycloaddition. The configuration of the adducts was determined by ^{1}H-nmr with nOe experiments. The kinetically controlled adducts always retain the configuration of the reacting dipolarophile but they can rearrange, sometimes under extremely mild conditions. The rearrangements were demonstrated to involve a 1,3-dipolar cycloreversion/ cycloaddition sequence since the intermediates were trapped by more reactive dipolarophiles.

Pursuing a research started by Grigg and coworkers[1] on 1,3-dipolar cycloadditions of azomethine ylides (AY), the reaction of these 1,3-dipoles derived from aminoacids and ninhydrin with (*E*)- and (*Z*)-2-oxoindolin-3-ylidene acetophenones was studied.[2]

#Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Since examples were reported[3] showing loss of configuration in some reactions with (*E*)-2-oxoindolin-3-ylidene acetates, the cycloaddition with the above stereoisomers was considered a useful tool to test a loss of stereoselectivity, totally unusual in 1,3-dipolar cycloaddition. When ninhydrin-derived AY reacted with (*E*)- or (*Z*)-2-oxoindolin-3-ylidene dipolarophiles, adducts always retained the configuration of the reagent. Under thermal conditions, nevertheless, some adducts derived from (*E*)-dipolarophiles rearranged to the thermodynamically stable regioisomer[4] through a 1,3-cycloreversion-cycloaddition reaction (Scheme 1).

Scheme 1



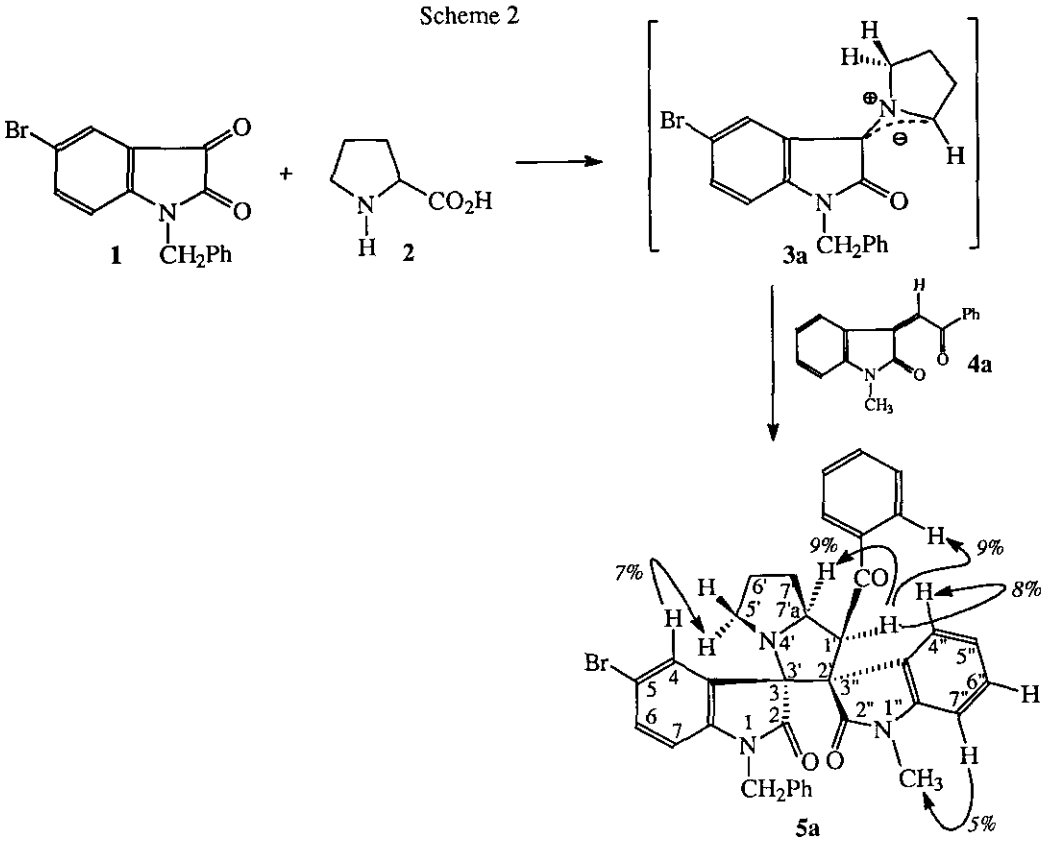
The AYs are known to give adducts loosing the configuration of the dipolarophile[3] derived from aminoacids and isatines. This reaction was hence tested with (*Z*)- and (*E*)-2-oxoindolin-3-ylidene acetophenones.

RESULTS

Reaction of azomethine ylide from isatin and proline. In order to label oxindole rings deriving from dipole (respectively from dipolarophile), suitable substituents were located on reagents. Thus 1-benzyl-5-bromoisatin (**1**) and proline (**2**), the precursors of AY (**3**), were made to react with (Z)-1-methyl-2-oxoindolin-3-ylidene acetophenone (**4a**). At room temperature the reaction was accomplished within 24 hours and 86% yield of a

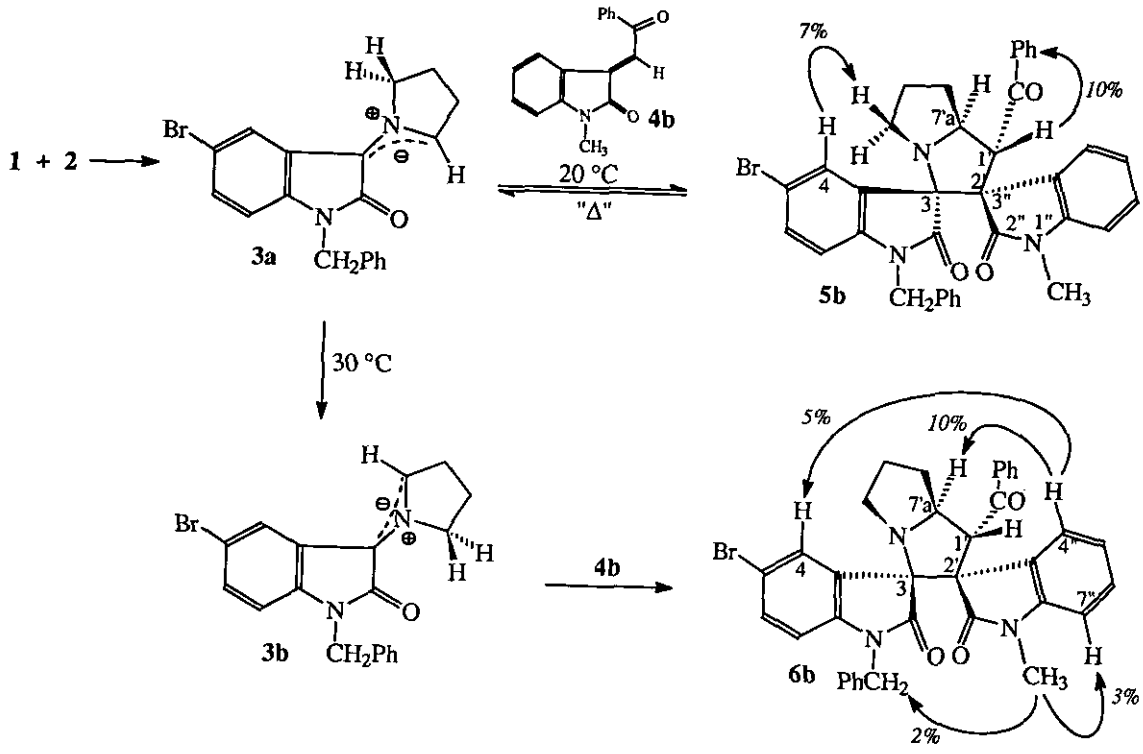
single adduct was obtained. By nmr it was shown to be 1-benzyl-5-bromo-2-oxoindol-3-spiro-2'-(1'-benzoylhexahydropyrrolizin)-3'-spiro-3"-(1"-methyl-2"-oxoindole) (**5a**) and nOe experiments (whose results are reported in the formula in Scheme 2) allowed to determine the relative configuration of the four stereocenters. This resulted to be [3R, 1'S, 2'S, 7'aS],[5] hence the configuration of **4a** was retained in **5a**.

Scheme 2



When the reaction was performed with (*E*)-1-methyl-2-oxoindolin-3-ylidene acetophenone (**4b**) again at room temperature (but avoiding the summer season!) the reaction was completed within 3 days and a single product (**5b**: mp 145-146 °C) was obtained in 73% yield (at 5 °C, same result in 12 days with 82% yield). Its purification must be performed very carefully (see Experimental) otherwise it is converted into a different product (**6b**: mp 209-211 °C) isomer of the former. **6b** can be obtained directly from **1**, **2**, and **4b** running the reaction at 30 °C (78% yield). Nmr experiments allowed to determine their structures and configurations (Scheme 3).

Scheme 3

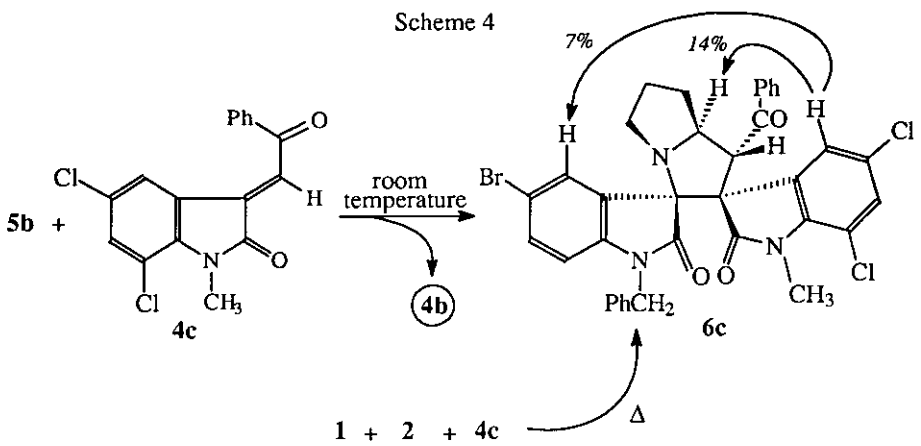


Both **5b** and **6b** are 1-benzyl-5-bromo-2-oxoindol-3-spiro-2'-(1'-benzoylhexahydropyrrolizin)-3'-spiro-3"-(1"-methyl-2"-oxoindole) (isomers of **5a**), but the configuration of their chiral centers is [**5b**: 3R, 1'R, 2'S, 7'aS] and [**6b**: 3S, 1'R, 2'S, 7'aS]. The crucial nOe effect characterizing **6b** is a 5% enhancement of H-4 obtained when H-4" was irradiated. Only a "head to head" facing of the oxindole rings is conceivable to this result, that is further supported by a 2% nOe between N-CH_3 and N-CH_2 oxoindolic groups.

The thermal conversion of **5b** into **6b** (and the formation of **6b** at 30 °C) could involve either the cleavage of the C2'-C3 bond with formation of a zwitterion that cyclizes, or a 1,3-dipolar cycloreversion[2] to **4b** and **3a**, the latter isomerizing into its configurationally distinct isomer (**3b**), that reacts to give the thermodynamically stable adduct (**6b**).

The 1,3-dipolar cycloreversion-cycloaddition pathway was demonstrated by treating **5b** in the presence of (*E*)-5-chloro-1-methyl-2-oxoindolin-3-ylidene acetophenone (**4c**). This was partly captured by **3b** to give the new adduct (**6c**) in 48% yield, whereas **4b** was released and isolated (Scheme 4).

Scheme 4



6c was obtained in high yield at room temperature from **1**, **2**, and **4c**, and nOe experiments, reported in Scheme 4, are in agreement with its [3S, 1'R, 2'S, 7'aS] configuration.

Reaction of azomethine ylide from isatin (1) and sarcosine. Sarcosine (**7**) and isatin (**1**), through a dipolar intermediate that loses carbon dioxide,[2] give AY (**8**). The reactions with either **4a** or **4b** require 3 days at room temperature and the same adduct (**9**) is obtained from both isomers. The nmr spectrum reveals that **9** is 1-benzyl-5-bromo-2-oxoindol-3-spiro-2'-(4'-benzoyl-1'-methylpyrrolidin)-3'-spiro-3"-(1"-methyl-2-oxoindole) and ^{1}H-NOESY experiments do not show the significant relationship between H-4 and H-4" that would suggest a "head to head" facing of the oxindole rings.

If 1,3-dipolar cycloaddition occurs with retention of configuration and **9** is a primary reaction product, either **4a** or **4b** must isomerize under the experimental conditions and the $k_{isom.}$ must be significantly faster than $k_{cyc.}$ of the unstable isomer.

Therefore the reaction was studied kinetically by uv-vis spectroscopic analysis. In the presence of **8**, **4a** does not react but isomerizes and the second order rate constant in ethanol at 25 °C is $k_{isom.\ 4a} = 8.8 \times 10^{-2}$ (l mol^{-1} s^{-1}), while **4b** gives 1,3-dipolar cycloaddition with a second order rate constant (ethanol, 25 °C) $k_{cycl.\ 4b} = 1.7 \times 10^{-3}$ (l mol^{-1} s^{-1}). Thus the isomerization of **4a** to **4b** is 52 times faster than the 1,3-dipolar cycloaddition of the latter.

The effect of this significant difference is observed in Figure 1. **A** and **B** are the times courses of the uv-vis spectra of two solutions: the former contains **4a** and **8** in a ratio of 1:2, the concentrations of **4a** and **4b** are identical. **A** increases the absorbance (isomerization of **4a** to **4b**), **B** decreases the absorbance (cycloaddition of

4b); after 9 h the uv-vis spectra are nearly superimposable and also A begins now to decrease with the same rate of B.

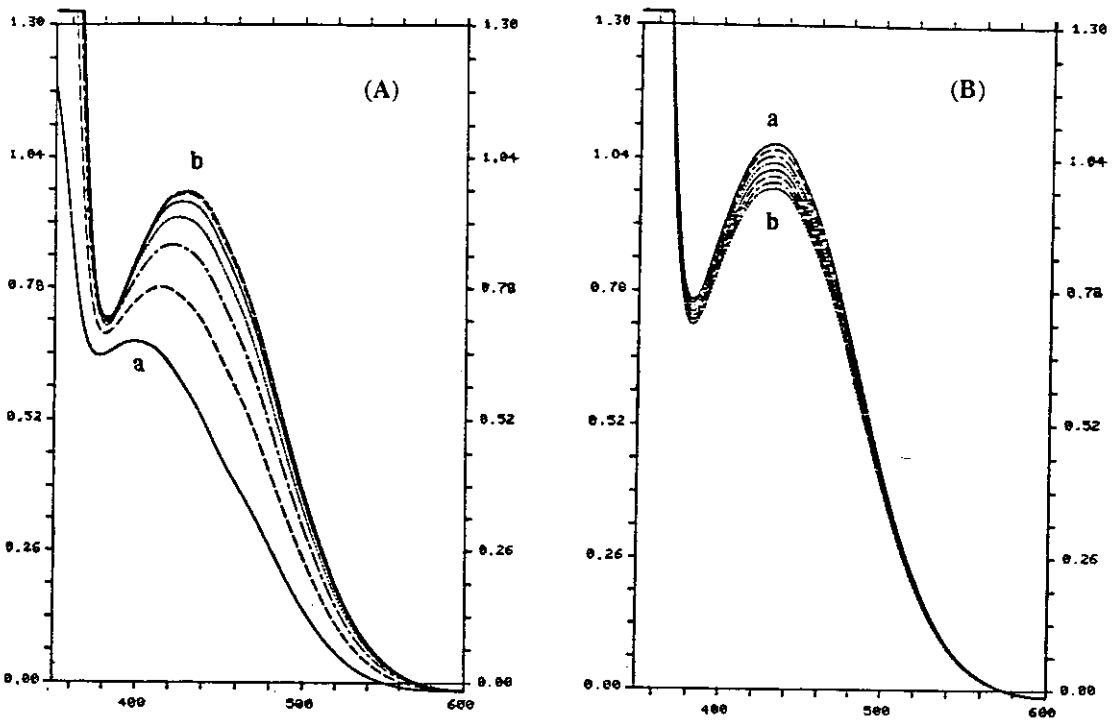
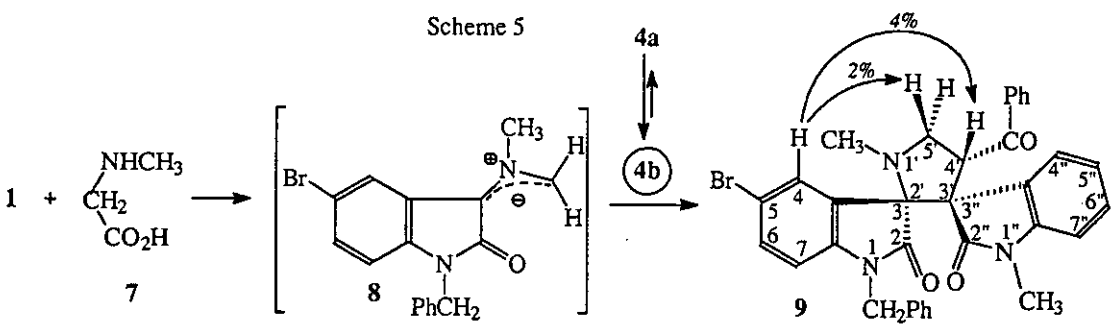


Figure 1. Time course of the reaction of **8** with **4a** (**A**) and **4b** (**B**): the **a** curve is the uv-vis spectrum at time 0, the **b** cuve after 560 minutes.

These results are summarized in Scheme 5. The [3R, 3'S, 4'S] configuration of **9**, only suggested by the small values of nOe effects observed, was fully confirmed by an x-ray analysis.

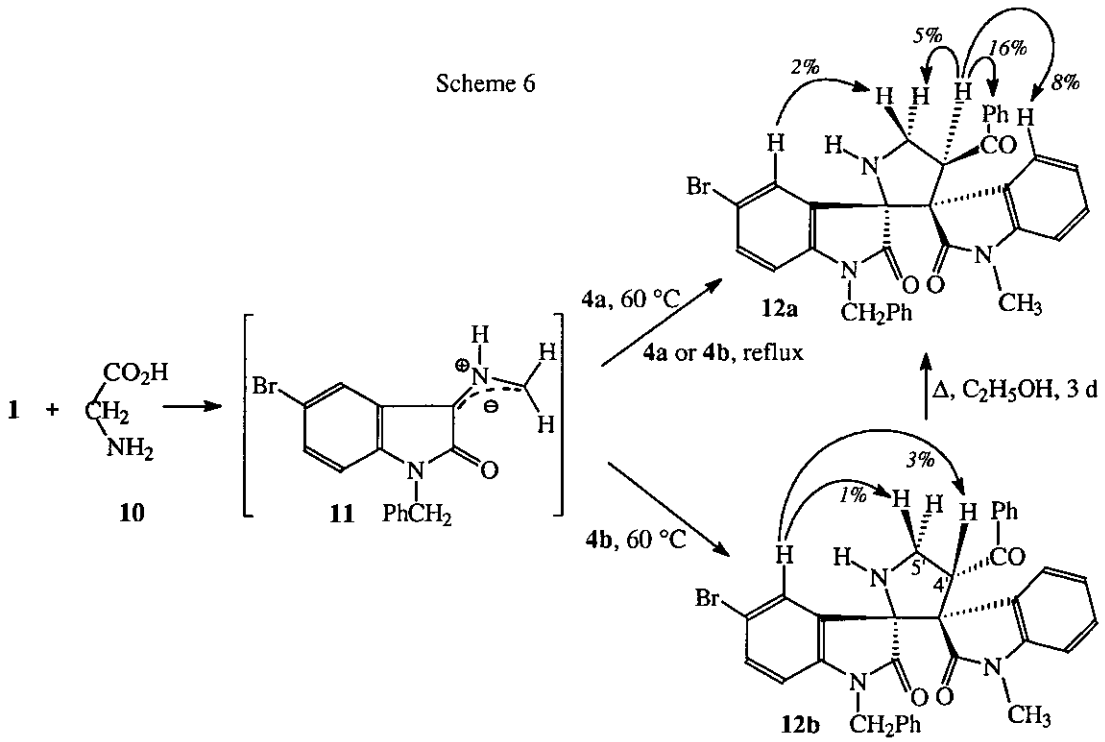
Scheme 5



Reaction of azomethyne ylide from isatin (1) and glycine. The reaction of **1**, glycine (**10**), and the dipolarophiles may occur with or without loss of carbon dioxide,[6,7] depending on the experimental conditions: higher temperatures favour the formation of the decarboxylated dipole.

The optimum temperature to avoid mixtures again containing undecarboxylated adducts is 60 °C, thus the reactions with **4a** and **4b** were performed under these experimental conditions that involve the formation of AY (**11**). Both reactions occur without any isomerization of the dipolarophile: **4a** gave a single adduct (**12a**), **4b** gave **12b** that separated out from the reaction mixture. Both products were found to be 1-benzyl-5-bromo-2-oxoindol-3-spiro-2'-(4'-benzoylpyrrolidin)-3'-spiro-3"-(1"-methyl-2-oxoindoles). The nOe experiments, reported in Scheme 6, assigned the [3R, 3'S, 4'R] configuration to **12a** and the [3R, 3'S, 4'S] configuration to **12b**; thus both adducts retain the configuration of their corresponding dipolarophiles.

Scheme 6

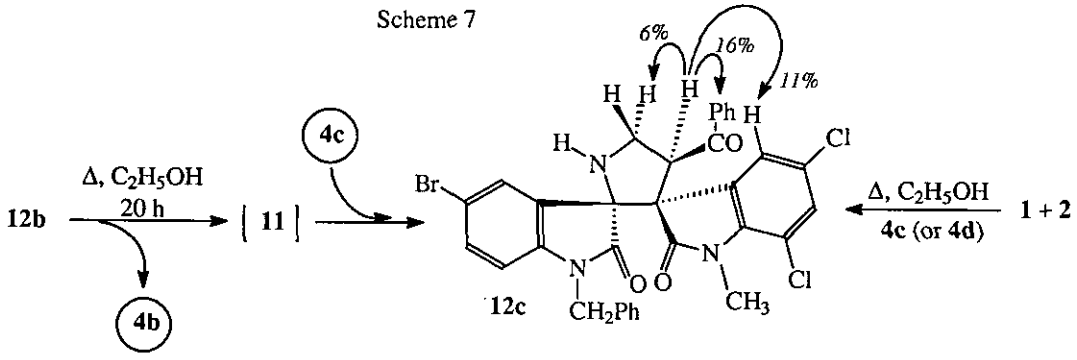


If the reactions are run in refluxing ethanol, the result is quite different, and both **4a** and **4b** gave the same product (**12a**). Therefore this is the thermodinamically stable adduct of **4b** whereas **12b** is formed under

kinetically controlled conditions. This was easily checked since **12b** cleanly converted to **12a** when refluxed three days in ethanol.

This rather unusual isomerization may occur either by proton loss and gain of H-4', or by cleavage of the C4'-C5' bond giving rise to a stabilized zwitterion, or by 1,3-dipolar cycloreversion giving **11** and **4b** with the latter product equilibrating with its isomer (**4a**) under the thermal conditions. The first option was excluded because no deuterium incorporation was observed running the isomerization in C_2H_5OD. The last pathway was supported by the following experiment. The unstable isomer (**12b**) was heated in refluxing ethanol with an equimolecular amount of **4c**. After 20 hours the reaction mixture was found to contain (besides a small amount of **12a**) **4b**, formed by the 1,3-dipolar cycloreversion, and a new adduct (**12c**), incorporating **4c**, that was the result of a new 1,3-dipolar cycloaddition between AY (**11**) and the new (and more reactive) dipolarophile (**4c**). The nmr revealed **12c** has a [3R, 3'S, 4'R] configuration, hence a formal loss of the configuration of **4c** was accomplished. This is again due to the experimental conditions, since the reaction of **1**, **2**, and **4c** (or its *Z* isomer **4d**) gave the same **12c** above described (Scheme 7).

Scheme 7

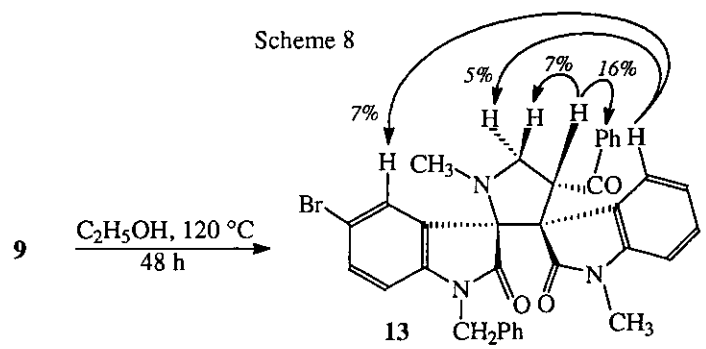


DISCUSSION

Is **9**, the product of both **4b** and **4a** with sarcosine-AY (**8**), an adduct with a stable configuration or is it only the result of a kinetically controlled 1,3-dipolar cycloaddition? The experiment supports its stability (no other product was obtained from **4a** or **4b**), the above results cast doubt on this.

When **9** was heated into a sealed vial in ethanol (48 h, 120 °C), it cleanly converted into its isomer (**13**), whose configuration, by nOe experiments reported in Scheme 8, was found to be [3R, 3'R, 4'S], hence with "head to head" facing of the oxindole rings.

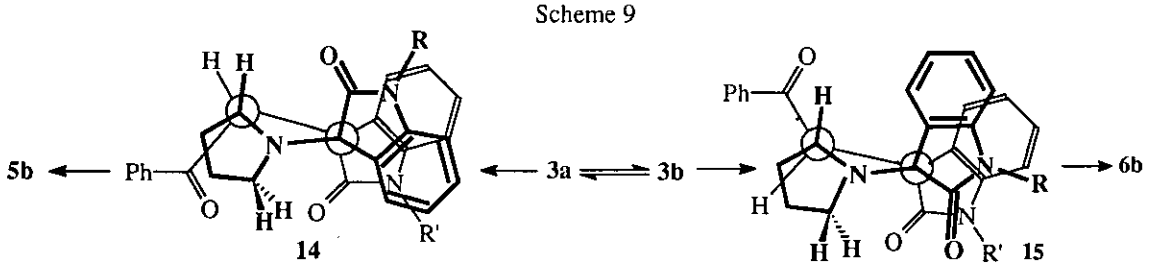
Scheme 8



The overall balance of 1,3-dipolar cycloadditions of AYs with 2-oxoindolin-3-ylidene acetophenones could be rationalized since both *E* and *Z* isomeric dipolarophiles were available and their reactivity was hence studied in details.

A loss of configuration of the dipolarophile in an AY-cycloadduct can be the result of an equilibration of the oxoindolidene derivative. This occurs with *Z*-isomer (**4a**) when it reacts with sarcosine-AY (**8**). It does not occur either with **3** or with **11**. It is nevertheless important to run the reactions when the aminoacid has already given rise to the AY, otherwise isomerizations would be much more diffused: proline causes isomerization of **4a**, its ylide (**3**) not. Thus 1,3-dipolar cycloadditions of AY and oxoindolidene derivatives always occur with retention of configuration of the dipolarophile to give a kinetically controlled product. This can rearrange under more or less severe conditions to a differing isomer through 1,3-dipolar cycloreversion/cycloaddition sequence. The configurations of the stereocenters of **5** and **6** are due to the steric interactions developed by the proline ring in the transition state. Thus, **3a** is the kinetically formed AY[1] that reacts with **4b** through the less congested transition state (**14**) to give the kinetically controlled adduct (**5b**). The reaction of **3b** with **4b**, to give the thermodynamically stable isomer (**6b**), again involves the less hindered transition state that now is **15** (Scheme 9).

Scheme 9



The isomerization of sarcosine-AY adducts (**9**) *vs* (**13**), though occuring under much more severe conditions, can be rationalized with a somewhat similar approach.

Finally, the formation of kinetic *vs* thermodinamic adducts of glycine-AY has a different origin. Again it is the result of a 1,3-dipolar cycloreversion/cycloaddition sequence, but involving a thermal equilibration of the dipolarophile also.

In conclusion, these reactions must be carefully run under conditions preventing any isomerization, otherwise adducts can be obtained that, at a first glance, may appear as a proof of a non-concerted character of the cycloaddition.

EXPERIMENTAL

Melting points were determined by the capillary method. Elemental analyses were obtained with a C. Erba mod. 1106 CHN analyzer. ^{1}H-Nmr spectra were recorded on a Bruker 300 spectrometer, ir spectra (nujol mulls) on a Perkin Elmer 983 spectrophotometer. The stationary phase for the column chromatography was Merck silica gel (230-400 mesh ASTM).

Reaction of azomethyne ylides and 2-oxoindolin-3-ylideneacetophenones. General method. A mixture of equimolecular amounts (5 mmol) of isatin (**1**), aminoacid (**2** or **7** or **10**) and 2-oxoindolin-3-ylidene acetophenones (**4a-c**) in 98% aqueous ethanol (7.5 ml) was stirred under the conditions reported in Table 1. In general the product separated out was filtered, while in the case of **12a** the solvent was evaporated and the residue was crystallized. The physical characteristics and the elemental analyses of each adduct are reported in Table 1, their ^{1}H-nmr spectra in Table 2.

Rearrangement reactions of the adducts (5b, 9 and 12b). General method. A solution of the unstable adduct (**5b** or **9** or **12b**) (0.5 mmol) in ethanol (5 ml) was heated under the conditions described in Table 3. Upon cooling or by concentration of the solvent, the isomerized adduct separated, whose analytical and spectral data are identical to those of a sample when already described.

Reaction of 5b and 4c. A mixture of equimolecular amounts of **5b** (1 mmol) and **4c** was stirred in EtOH (25 ml) 20 days at room temperature. The white solid separated (62% yield) was filtered and found (by nmr) to be a mixture of **6c** and **6b** in a ratio 3:1. **6c** can be isolated by fractional crystallization with AcOEt and its physical

and spectral data are identical with a sample synthesized as above. The reaction mother liquors were evaporated and the residue was column chromatographed (eluant, CH_2Cl_2) and unreacted **4c** (18% yield) and **4b** (72% yield) were isolated in the order.

Table 1. Reaction conditions, physical characteristics, and elemental analyses of adducts (**5a,b**, **6b,c**, and **12a-c**)

Product	T/°C	time	yield (%)	mp, °C (solvent)	ir, cm^{-1} $\nu_{C=O}$	Formula	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
5a	20	24 h	86	192 (EtOH)	1715-1710 1680	$C_{36}H_{30}N_3O_3Br$	68.36	4.78	6.64	68.15	4.57	6.68
5b	20	3 d	73	145-6 (MeOH)[a]	1725-1700 1680	$C_{36}H_{30}N_3O_3Br$	68.36	4.78	6.64	68.50	4.79	6.63
6b	30	3 d	78	209-11 (EtOH)	1721-1705 1680	$C_{36}H_{30}N_3O_3Br$	68.36	4.78	6.64	68.76	4.93	6.77
6c	20	2 h	85	197 dec. (AcOEt)	1726-1710 1680	$C_{36}H_{28}N_3O_3BrCl_2$	61.64	4.02	5.99	61.59	4.00	5.93
9[b]	20	3 d	86	188 (EtOH)	1715-1686	$C_{34}H_{28}N_3O_3Br$	67.33	4.65	6.93	67.65	4.49	6.91
12a[c]	60	3 h	70	193 (d)	1704-1675	$C_{33}H_{26}N_3O_3Br$	66.89	4.42	7.09	66.61	4.33	7.05
12b	60	3 h	69	195-7 (e)	1781-1691	$C_{33}H_{26}N_3O_3Br$	66.89	4.42	7.09	66.37	4.51	7.27
12c	78	4 h	74	232-3 dec.	1710-1700	$C_{33}H_{24}N_3O_3BrCl_2$	59.93	3.66	6.35	59.89	3.60	6.33

[a] Dissolved at 20 °C, concentrated under vacuum and chilled;[b] from **4b**; from **4a** same conditions, yield about 80%;[c] from **4a**; from **4b** 3 days under reflux (86%);[d] dissolved in hot benzene and crystallized upon dilution with cyclohexane;[e] analyzed as uncrystallized product.

Table 2. ^{1}H-Nmr data of compounds[a]

	5a	5b	6b	6c	9[b]	12a	12b	12c	13
CH_2-1	4.47 d	4.11 d	4.92 d	4.81 d	4.30 d	4.58 d	4.26 d	4.58 d	4.78 d
	5.12 d	5.05 d	5.00 d	4.87 d	4.80 d	5.01 d	4.93 d	5.12 d	4.90 d
H-4	7.84 d	7.90 d	6.63 d	6.64 d	7.78 d	7.61 d	7.68 d	(c)	6.17 d
Me-1'	----	----	----	----	2.16 s	----	----	----	2.18 s
H-1'	5.73 d	4.54 d	5.43 d	5.45 d	----	----	----	----	----
H-4'	----	----	----	----	4.88 dd	5.62 dd	4.72 t	5.64 dd	5.35 dd
H-5'α[d]	(c)	3.90 m	(c)	(c)	4.69 t	4.25 t	5.01 dd	4.26 t	4.26 dd
H-5'β[d]	(c)	3.00 m	(c)	(c)	3.41 dd	3.80 dd	3.75 dd	3.74 dd	3.70 dd
H-7'a	4.97 m	5.70 m	4.80 m	4.65 m	----	----	----	----	----
Me-1"	3.26 s	2.83 s	2.40 s	2.81 s	2.80 s	3.26 s	3.00 s	3.62 s	2.40 s
H-4"	7.27 dd	(c)	7.87 dd	7.80 dd	(c)	7.15 dd	(c)	7.24 d	7.50 dd
H-7"	(c)	(c)	6.38 dd	----	----	----	----	----	----
o-COH[e]	(c)	(c)	(c)	(c)	(c)	7.90 m	(c)	7.91 m	7.10 m
$J_{1',7'a}$[f]	10	9.5	8.0	8.2	----	----	----	----	----
$J_{4',5'\alpha}$[f]	----	----	----	----	9.3	11.0	8.0	11.0	5.5
$J_{4',5'\beta}$[f]	----	----	----	----	7.5	9.0	8.0	9.0	10.0
$J_{4'\alpha,5'\beta}$[f]	----	----	----	----	9.0	11.5	12.0	11.0	9.0

[a]$CDCl_3$ as solvent; [b]acetone *d*-6 as solvent; [c]not determined; [d]α and β are referred to formulae in their respective schemes; [e]*ortho* aromatic protons in the 4'-benzoyl group; [f]*Hz*.

Table 3. Experimental conditions and results of the rearrangements.

Starting product	Rearranged product	T/°C	Time	Yield (%)
5b	**6b**	78	10 min	70
9	**13**[a]	120	48 h	74
12b	**12a**	78	3 d	80

mp: 150 °C (from EtOH); ir: $\nu_{C=O}$; 1724, 1710, 1686 cm^{-1}. Elemental Anal. Calcd for $C_{34}H_{28}N_3O_3Br$: C, 67.33; H, 4.65, N, 6.93. Found: C, 67.02; H, 4.80; N, 6.88.

Reaction of 12b and 4c. A mixture of equimolecular amounts of **12b** (0.2 mmol) and **4c** was refluxed in ethanol (15 ml) for 20 h. The white solid separated (52% yield) was filtered and found (by nmr) to be a mixture of **12a** and **12c** (ratio 5:1); the latter product was separated by fractional crystallization with AcOEt. The mother liquors were chromatographed as above and, besides a small amount of unreacted **4c**, **4b** was separated in 57% yield.

Kinetic determinations. The overall reaction rates were measured by following the variation of the uv-vis absorption on a Perkin-Elmer Lambda 16 spectrophotometer provided with a thermostatted cell transport assembly and an automatic multicell programmer. The solutions were measured in 1.00 cm OS Hellma couvettes with 3 ml capacity and the rate constants were determined as follows. Two solutions were prepared by weighing accurately in 10 ml volumetric flasks, as far as possible, identical amounts of **4a** and **4b** and dissolving them in ethanol. In the specific example the concentrations were 5.06×10^{-3} M. A third solution, containing AY **8** in ethanol (in the same specific example the concentration was 5.44×10^{-3} M) was prepared by weighing accurate equimolecular amounts of isatin (**1**) and sarcosine (**7**) in a 10 ml volumetric flask. Four cells were filled with 0.3 solution of **4a** or **4b**, 0.6 ml solution of **8** and 1.5 ml of ethanol, all accurately measured with mycrosyringes. A reference cell was filled with 0.6 ml solution of **8** and 1.8 ml of ethanol. At time = 0 both the spectra and the absorbance at 430 nm of the cells, thermostatted at 25 °C, were registered. At time intervals of 120 min the variation of the absorbances and the change of the spectra (Fig. 1) were measured. The second order rate constants were then calculated with the standard procedures.

ACKNOWLEDGEMENTS

The financial support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Consiglio Nazionale delle Ricerche (CNR) is warmly acknowledged.

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Received, 18th October, 1993