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BASIC MEDIA BEHAVIOR OF N-[2-(1-HYDROXY-2-Y-ETHYL)PHENYL] ETHYL CARBAMATES (Y=SMe, SOMe, SO_2Me, H, Br, CN)

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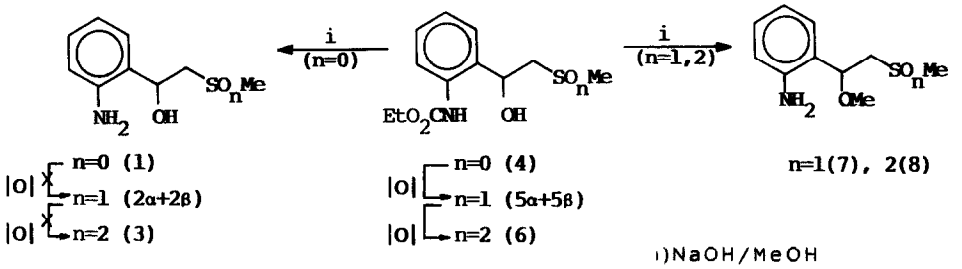
Abstract: From the results obtained in the hydrolysis reaction of the carbamate group of some thioderivatives compounds whose common structure is (2-EtOOCNH-C6H4)-CHOH-CH2Y a mechanism is suggested to explain the products, as well as the relationship between the relative configuration of diastereoisomeric sulfoxides (Y=SOMe) with the reaction rate and with the stereochemical outcome. Other interesting and unexpected products are yielded when the hydrolysis reaction of others carbamates (Y=H, Br, CN) is carried out. In the present cases, the carbamate function seems to behave as a very versatile group capable of readily undergoing conversions to several kinds of heterocycles.

INTRODUCTION

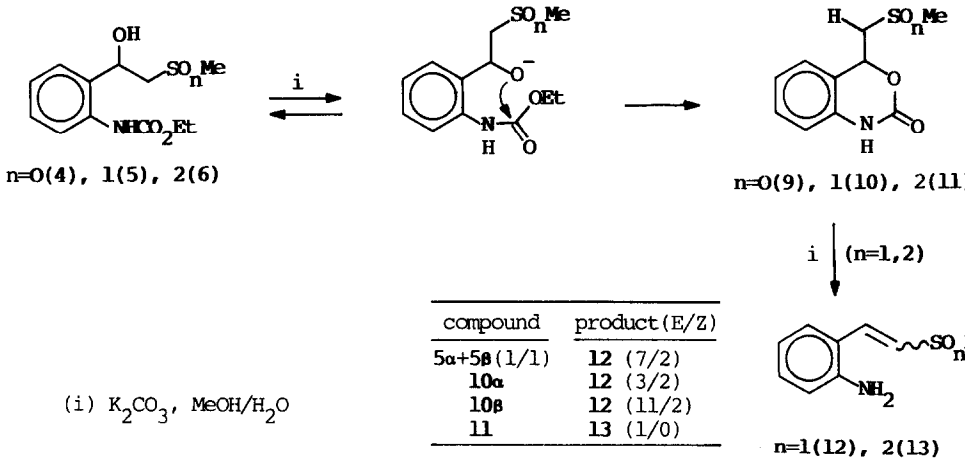
1-(2-Aminophenyl)-2-Y-ethanol [Y=SMe(**1**), SOMe(**2**) and SO_2Me(**3**)] were found among oxisuran bioisosters whose syntheses and conformational behavior were reported in a previous paper.[1] Attempts to prepare **2** and **3** through oxidation of **1** failed due to the presence of the amine group affected by the oxidizing agents. This problem was avoided by using the ethyl carbamate as protecting amine group, which enabled us to achieve the aforementioned oxidations. Thus, it was possible to obtain the pair of diastereomeric sulfoxides (**5α** and **5β**) and the sulfone (**6**) from **4** (scheme 1). Nevertheless, the deprotection of the amine group using the basic conditions reported in the literature[2] did not yield the expected amino-derivatives in all cases, making it necessary to change the synthetic strategy in order to obtain **2α**, **2β** and **3**[1]. In this paper we propose to study the anomalous reactions of these carbamates in basic media. The interest of this kind of reactions lies in the intramolecular participation of the hydroxylic group in the hydrolysis reaction, which accounts for the mildness of the conditions of the reaction unable to affect other carbamate groups which do not present the hydroxylic function in the appropriate position.



Scheme 1

RESULTS AND DISCUSSION

The standard conditions employed for the hydrolysis of carbamates to amines involve refluxing of the substrate with NaOH in MeOH.[2] Thioether behaves in the usual manner affording the hydroxythioether **1** whilst compounds **5** and **6** yielded surprisingly the corresponding methoxy-derivatives **7** and **8**.[1] This transformation implies the replacement of the OH group by the OMe and only can be rationalized assuming the previous dehydration of the substrate to the vinylsulfoxide or vinylsulfone, which undergo nucleophilic addition of the solvent. Dehydration of the thioether



(i) K_2CO_3, $MeOH/H_2O$

compound	product(E/Z)
5α+5β(1/1)	**12** (7/2)
10α	**12** (3/2)
10β	**12** (11/2)
11	**13** (1/0)

Scheme 2

is not possible due to the lower acidity of the hydrogen atoms adjacent to the sulfur function, giving rise to the usual reaction product.

To prove this hypothesis, we treated the carbamates with weaker bases. Thus, when the sulfone **6** was treated with diluted K_2CO_3 at room temperature *(E)-2-aminostyryl methyl sulfone* **13** was obtained exclusively (scheme 2). It is surprising that such a weak base was able to hydrolyze the carbamate as well as dehydrate the vinylsulfone, taking into account that neither reactions takes place if only one of the functionalities is present. The mixture of the hydroxysulfoxides **5α** and **5β** undergoes a

similar transformation,furnishing a mixture of the geometric isomers of the corresponding vinylsulfoxides *(E)*-**12** + *(Z)*-**12**. Finally the thioether **4** was converted into the benzoxazine **9**, without the corresponding olefin being detected. The latter result suggests the mechanism shown in the scheme 2, which accounts for the interaction between the OH and the carbamate group.

The alkoxide ion generated by means of the base (K_2CO_3) attacks the ethyl carbamate intramolecularly, giving the cyclic carbamate (**9**-**11**). In sulfoxide and sulfone the acidity of the proton adjacent to the sulfur atom is sufficient to be abstracted by the base yielding the olefins directly. Intermediates **10** and **11** are not observed among the reaction products. On the contrary, in the case of thioether, the acidity is much lower and, consequently, the reaction stops in the cyclic carbamate stage (**9**).

To give evidence of the postulated mechanism, compounds **10** and **11** were prepared by oxidation of **9**. Sulfoxide **10** was obtained as a mixture of diastereoisomers (α and β), which can be separated by chromatography. These compounds were independently treated with K_2CO_3, leading to the same olefins *(E)*-**12** + *(Z)*-**12** obtained in the reaction of **5α** and **5β**. The relative proportions of the geometric isomers in the reaction products changed depending on the relative configuration of the starting sulfoxide (see scheme 2). In the same way, from the ^{1}H-nmr control of the reaction it can be stated that β isomer reacts more rapidly than its α epimer. The treatment of the benzoxazine sulfone **11** with K_2CO_3 gave rise to olefin **13** as the only product. These experiences suggest that benzoxazines **10** and **11** must be reaction intermediates.

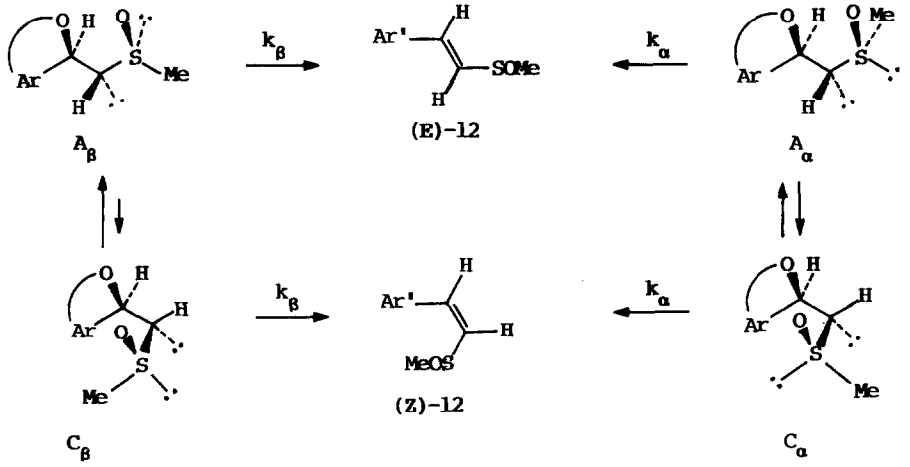
The reactions of **5α**, **5β** and **6** with K_2CO_3 were conducted removing aliquots at intervals and analyzing them by ^{1}H-nmr. From these experiences it could be established that the reaction proceeds through the benzoxazines. Moreover, the relative configuration of the chiral centers remains unaffected in the course of the reaction. Thus, **10α** and **10β** are the only products obtained from **5α** and **5β** respectively.

So the proposed mechanism accounts for all the results, though the relationship between the relative configuration and the reaction rate of sulfoxides and the stereochemical outcome of the reaction are the only aspects to be explained, both of which requires knowing the relative configuration of the starting carbamates.

The configurational assignment of diastereoisomeric sulfoxides **5α**, **5β**, **10α** and **10β** was made on the basis of their different conformational behavior (see reference 3 and table 1) as could be stated for other hydroxysulfoxides with similar structure.[1,4]

This study led us to propose the configuration (RR, SS) for isomers α and (RS, SR) for β. This assignment is also supported by the experimental melting points of the hydroxysulfoxides, higher in **5α** than in **5β** (it has been established in other compounds of similar structure that isomers α usually exhibit the highest melting points[5]).

Taking into account the acidity of the hydrogens adjacent to sulfinylic sulfur, it is likely that the elimination proceeds through an $E1_CB$ mechanism. This process requires an *anti* relationship between the carbanionic electron pair and the leaving group, in this case the oxygen atom. It is known that the most stable configuration of the α-sulfinylic carbanions in polar protic media is that which displays the sulfinylic oxygen in a spatial *anti* arrangement with the carbanionic pair.[6] Consequently, A and C (scheme 3) are the most stable conformation through which the elimination can take place since the carbanionic pair is simultaneously located in an *anti* relationship with both oxygen atoms. In



Scheme 3

the case of the β diastereoisomer there is a clear difference in the relative stabilization of such rotamers. Thus, the conformation C_β is strongly unfavorable [$(Ar/Me)_{1,3-p}$ interaction] compared with A_β. As a consequence *(E)*-**12** is expected to be the major product of the reaction. However, the stability differences between conformation A_α and C_α are less important, so it seems reasonable to obtain similar proportions of the *(E)*-**12** and *(Z)*-**12** isomers (see scheme 2). On the other hand, the higher stability of the A_β conformation with regard to A_α (the latter exhibits a $(Me/H)_{1,3-p}$ interaction non-existent in the former) can account for the higher observed rate of the reaction of the compound **10β** in relation to its diastereoisomer 10α.

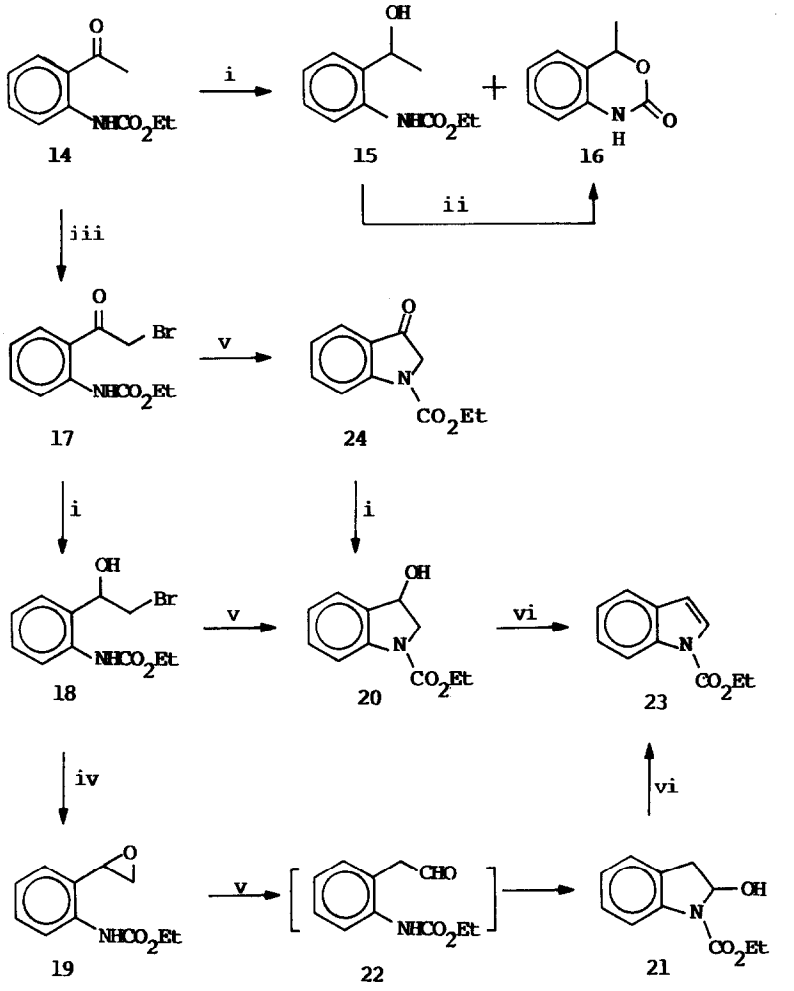
With regard to the sulfone, the stability differences between the geometric isomers *(E)*-**13** and *(Z)*-**13** must be much higher to the related sulfoxides since *(Z)*-**13** presents stronger steric interactions which can be relieved in the sulfoxides by the appropriate orientation of the electronic sulfur pair. In addition, rotamer A is now even more stable than C, which justifies that *(E)*-**13** was exclusively obtained from sulfone **11** (see scheme 3).

Taking into account the preceding data, the results obtained in the reactions of **4**, **5** and **6** under the usual conditions of carbamate hydrolysis (NaOH/MeOH and heat) it can be fully rationalized. At the first stage, all the compounds give rise to the corresponding benzoxazines, then, the thioether **9** undergoes hydrolysis by the action of the base, whilst sulfoxides **10** and sulfone **11** produce the olefins through loss of CO_2. The olefins undergo subsequent addition of methanol present in the medium. So the nature of the product is determined in the second step.

From the results of these kinds of reactions, we can suggest the easy formation of benzoxazines starting from any 1,3-aminoalcohol. In order to confirm this point we undertook the study of the reaction of other hydroxycarbamates. The reduction of ketone **14** with sodium borohydride yielded a mixture of the alcohol **15** and the benzoxazine **16**. As expected the overall conversion to **16** was carried out treating the previous mixture with K_2CO_3 (scheme 4). Much more interesting were the results obtained from the bromoderivative **18** (prepared by bromination of **14** and subsequent reduction of the carbonyl group of **17**). When this compound was treated with K_2CO_3, a complex mixture was obtained among which was identified epoxide **19**. This result involves the attack of the alkoxide group on the halide instead of on the carbamate function. Thus, treatment of **18** with the phase-transfer system NaOH/TBAI led to the epoxide **19** as the only reaction product in a 88% yield, whilst the reaction with NaH in THF afforded *N-ethoxycarbonyl-3-hydroxyindoline* **20** (90%). At first glance, it seems reasonable to admit that the obtention of **20** proceeds through epoxide **19** as the reaction intermediate, which can be subsequently open by the action of nitrogen. However, the latter mechanism can be ruled out since when epoxide **19** is treated with NaH in THF, *N-ethoxycarbonyl-2-hydroxyindoline*[7] **21** (88%) was surprisingly obtained. The formation of **21** can be rationalized assuming that the aldehyde **22** is the reaction intermediate[8] through which the carbamic nitrogen attacks the carbonyl group, furnishing compound **21**.

The spectral data and the results of the following chemical studies are consistent with the proposed structure of **20**. Treatment of both **20** and **21** with a catalytic amount of p-toluenesulfonic acid in toluene resulted

in the formation of the same compound **23**.[9] Moreover, the reaction of the α -bromoketone **17** with NaH in THF gave **24**, whose reduction with $NaBH_4$ yielded a compound identical with compound **20** obtained from **18**. Therefore, we can conclude on the basis of the high yield achieved that these reactions provide a useful entry into the synthesis of 2-, 3-hydroxyindolines (**20**, **21**) and 3-indolones (**24**).



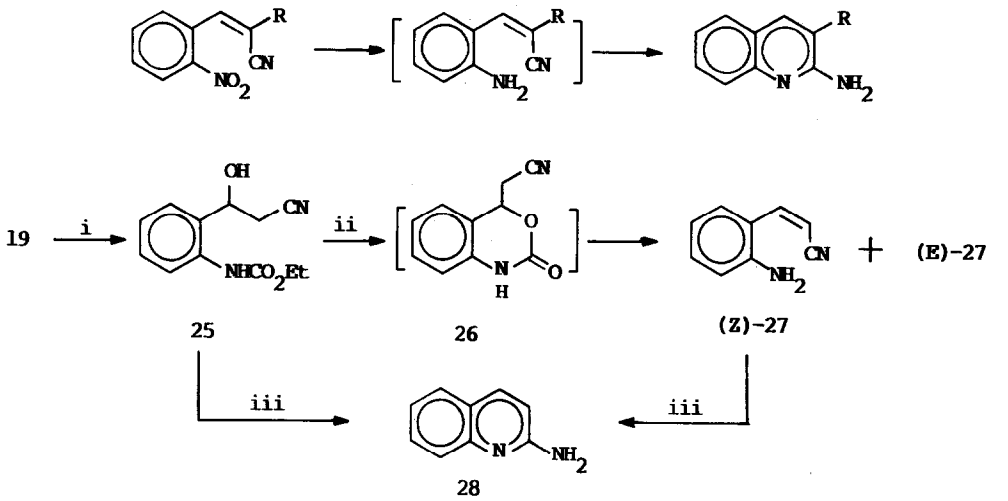
i)$NaBH_4$/THF; ii) K_2CO_3, MeOH/H_2O; iii) Br_2/Et_2O
iv) NaOHaq/TBAI/CH_2Cl_2; v)NaH/THF; iv) TsOH/Toluene

Scheme 4

These type of reactions can also be applied to the synthesis of 2-aminoquinoline. One of the first methods for its preparation is the reduction of the *2-nitrocinnamonitriles*.[10] In such a process the intermediate amine adds to the cyano group (scheme 5). The intermediate

amine can readily be generated from carbamate **25**, whose similar structure to sulfoxides **5** and sulfone **6** is obvious.

The synthesis of **25** was easily accomplished by treatment of the epoxide **19** with NaCN in DMF. When **25** is subject to the action of K_2CO_3, an equimolecular mixture of the expected olefins *(E)*-**27** and *(Z)*-**27** (93%) were produced, with it being possible to even detect the intermediate cyclic carbamate **26** by ^{1}H-nmr. When the mixture of olefins *(E)*-**27** and *(Z)*-**27** were allowed to stand at room temperature for approximately two months, the



i) NaCN/DMF; ii) K_2CO_3, MeOH/H_2O; iii)NaOH, MeOH/H_2O

Scheme 5

isomer *(Z)* is quantitatively converted into the 2-aminoquinoline. However, this transformation was achieved in 10 hours when NaOH is present. In both cases the *E* isomer remained unaltered. The reported yield of the synthesis of the 2-aminoquinoline are moderate in all cases.[11] However, 2-aminoquinoline can be obtained in 90% yield of the isolated product in just a single step from **25**, treating it with a deficiency of NaOH under reflux. It seems that the isomerization of the intermediate olefins takes place in the reaction conditions.

EXPERIMENTAL

Silica gel used in flash column chromatography was Merck-60 (230-400 mesh). Melting points were measured on a Büchi 594392 type S apparatus in open capillary tubes and are uncorrected. Mass spectra (MS) were determined in a HP-5985 spectrometer in the electron impact (EI) at 70 eV. Mass data are reported in mass unit (m/z) and the values in brackets refer to the relative intensity from the base peak (as 100%). The infrared

spectra were obtained on a Nicolet 5 DX FT-IR. The NMR spectra were recorded on a Bruker WP-200-SY spectrometer.

Treatment of Carbamates with potassium carbonate: General Procedure. To a solution of the corresponding carbamate derivative (7.8 mmol) in 20 ml of methanol 13 g (9.4 mmol) of a 10% aqueous potassium carbonate solution were added. The mixture was stirred for 10 hours at room temperature and diluted with 5 ml of water. After neutralizing with 10% hydrochloric acid the solution was extracted twice with methylene chloride, dried over sodium sulfate and the solvent removed under reduced pressure.

Treatment of Carbamates with sodium hydride: General Procedure. To a suspension of sodium hydride (1.80 mmol) in dry THF (20 ml) under argon atmosphere the corresponding carbamates **17**, **18** and **19** (1.80 mmol) in dry THF (10 ml) were added. The mixture was stirred for 4 hours at room temperature, diluted with water (1 ml) and neutralized with 10% hydrochloric acid. Usual work up yielded solids, which were crystallyzed.

4-Methylthiomethyl-1,4H-3,1-benzoxazin-2-one (**9**). It was obtained from **4**[1] by treatment with potassium carbonate. It was purified by column chromatography using methylene chloride/methanol (20/1) as eluent, yield 93%, mp 70-1°. (Found: C 57.60, H 5.28, N 6.84, S 15.01. $C_{10}H_{11}NO_2S$ requires C 57.40, H 5.30, N 6.69, S 15.32). ν_{max}(KBr) 3200, 2900, 1710, 1670, 1600, 1280, 1040, 750 cm^{-1}. m/z 209 M^+ (21), 163 (8), 148 (100), 120 (10), 92 (9), 77 (9), 61 (9). ^{1}H-δ($CDCl_3$) 9.45 (s, broad, 1H, NH), 7.28 (dt, J=1.7 and 7.7 Hz, 1H, H-6), 7.17 (dd, J=1.7 and 7.7 Hz, 1H, H-8), 7.07 (dt, J=1.2 and 7.7 Hz, 1H, H-7), 6.88 (dd, J=1.2 and 7.7 Hz, 1H, H-5), 5.54 (m, 1H, H-4), 3.03 (m, 2H, CH_2-S), 2.12 (s, 3H, CH_3S). ^{13}C-δ($CDCl_3$) 152.3 (CO), 135.0 (C-8a), 129.4 (C-7), 125.1 (C-5), 123.2 (C-6), 119.8 (C-4a), 114.5 (C-8), 79.6 (C-4), 39.5 (CH_2), 16.8 (CH_3).

4-Methylsulfinylmethyl-1,4H-3,1-benzoxazin-2-one (**10α** and **10β**). They were obtained as an equimolecular mixture by the oxidation of **9** with sodium metaperiodate following general methods outlined in the literature[12]. Yield 83%. Pure **10α** could be isolated by successive crystallizations from chloroform of the reaction mixture, mp 184-6°. (Found: C 53.54, H 4.67, N 6.12, S 14.48. $C_{10}H_{11}NO_3S$ requires C 53.32, H 4.92, N 6.22, S 14.23). max(KBr) 3100, 2940, 1725, 1600, 1500, 1280, 1040, 760 cm^{-1}. m/z 162 M^+-SOMe (29), 148 (12), 133 (45), 117 (48), 106 (14), 91 (26), 63 (22), 43 (100). ^{1}H δ(DMSO-d_6) 10.28 (s, broad, 1H, NH), 7.30 (m, 2H, H-6 and H-8), 7.05 (dd, J=1.1 and 7.6 Hz, 1H, H-7), 6.90 (dd, J=1.1 and 7.6 Hz, 1H, H-5), 5.73 (m, 1H, H-4), 3.32 (m, 2H, CH_2), 2.64 (s, 3H, CH_3). ^{13}C-δ(DMSO-d_6) 150.1 (CO), 135.8 (C-8a), 129.3 (C-7), 124.5 (C-5), 122.7 (C-6), 119.4 (C-4a), 114.1 (C-8), 72.7 (C-4), 58.3 (CH_2), 38.7 (CH_3). The evaporation of the mother liquors and crystallization of the residue from ethyl acetate afforded pure **10β**, mp 144-6°. ν_{max}(KBr): 3100, 2990, 1720, 1600, 1500, 1380, 1285, 1000, 760 cm^{-1}. m/z 162 M^+-SOMe (100), 148 (30), 133 (82), 117 (66), 106 (21), 90 (32), 77 (17), 65 (23), 43 (5). ^{1}H-δ(DMSO-d_6) 10.29 (s, broad, 1H, NH), 7.29 (m, 2H, H-6 and H-8), 7.05 (dt, J=1.0 and 7.7 Hz, 1H, H-7), 6.91 (dd, J=1.0 and 7.7 Hz, 1H, H-5), 5.80 (m, 1H, H-4), 3.36 (m, 2H, CH_2), 2.69 (s, 3H, CH_3). ^{13}C-δ(DMSO-d_6) 150.4 (CO), 135.7 (C-8a), 129.3 (C-7), 124.7 (C-5), 122.6 (C-6), 119.4 (C-4a), 114.2 (C-8), 72.9 (C-4), 56.3 (CH_2), 38.5 (CH_3).

4-Methylsulfonylmethyl-1,4H-3,1-benzoxazin-2-one (11). It was obtained by oxidation of an equimolecular mixture of **10α** and **10β** with hydrogen peroxide at 0° in TFA as the solvent. Yield 70%, mp 214-6°. (Found: C 49.50, H 4.49, N 5.66, S 13.18. $C_{10}H_{11}NO_4S$ requires C 49.78, H 4.59, N 5.80, S 13.29). ν_{max}(KBr) 3100, 2920, 1725, 1600, 1500, 1300, 1125, 1055, 755 cm^{-1}. m/z 241 M^+ (5), 197 (19), 161 (49), 148 (11), 133 (44), 117 (100), 91 (47), 77 (11), 65 (23), 44 (11). ^{1}H-δ(DMSO-d_6) 9.65 (s, broad, 1H, NH), 7.28 (m, 2H, H-6 and H-8), 7.01 (dt, J=1.3 and 7.6 Hz, 1H, H-7), 6.91 (dd, J=1.3 and 8.0 Hz, 1H, H-5), 6.37 (m, 1H, H-4), 4.33 (m, 2H, CH_2), 3.09 (s, 3H, CH_3). ^{13}C-δ(DMSO-d_6) 149.6 (CO), 135.6 (C-8a), 129.4 (C-7), 124.9 (C-5), 122.6 (C-6), 118.4 (C-4a), 114.1 (C-8), 73.5 (C-4), 57.5 (CH_2), 42.9 (CH_3).

2-Aminostyryl methyl sulfoxide ((E)-12 and (Z)-12)). They were obtained as a mixture from **5** or **10** (see scheme 2) by treatment with potassium carbonate. Yield 87%. Pure (Z)-**12** was isolated by crystallization of the mixture from methylene chloride, mp 184-5°. (Found: C 59.50, H 6.00, N 7.65, S 17.48. $C_9H_{11}NOS$ requires C 59.63, H 6.12, N 7.73, S 17.69). ν_{max}(nujol): 3416, 3219, 1644, 1602, 1159, 1018, 962, 941, 772, 744, 723 cm^{-1}. m/z M^+ 181 (6), 166 (3), 148 (11), 133 (2), 117 (100), 106 (7), 89 (21), 65 (13), 52 (7). ^{1}H- δ(DMSO-d_6) 7.15 (d, J=10.0 Hz, 1H, $\underline{CH}C_6H_4$), 7.06 (ddd, J=1.6, 7.3 and 8.1 Hz, 1H, H-4 C_6H_4), 6.95 (dd, J=1.6 and 7.7 Hz, 1H, H-6 C_6H_4), 6.66 (dd, J=1.2 and 8.1 Hz, 1H, H-3 C_6H_4), 6.53 (ddd, J=1.2, 7.3 and 7.7 Hz, 1H, H-5 C_6H_4), 6.51 (d, J=10.0 Hz, 1H, $\underline{CH}SO$), 5.34 (s, broad, 2H, NH_2), 2.70 (s, 3H, CH_3). ^{13}C- δ(DMSO-d_6) 146.9 (C-2), 136.2 (C-6), 134.7 ($\underline{CH}C_6H_4$), 130.6 ($\underline{CH}SO$), 130.0 (C-4), 118.0 (C-1), 115.4 (C-5), 114.9 (C-3), 39.7 (CH_3). The E isomer could be isolated as an oil by chromatography of the evaporated mother liquors of crystallization using methylene chloride/methanol (20/1) as eluent. ν_{max}(film) 3360, 3240, 3020, 1640, 1610, 1490, 1460, 1320, 1260, 1030, 965, 755 cm^{-1}. m/z 181 M^+ (8), 166 (3), 148 (10), 118 (28), 117 (100), 106 (5), 90 (23), 77 (7), 63 (11), 51 (7). ^{1}H-δ(DMSO-d_6) 7.34 (dd, J=1.6 and 7.5 Hz, 1H, H-6 C_6H_4), 7.29 (d, J=15.3 Hz, 1H, $\underline{CH}C_6H_4$), 7.10 (d, J=15.3 Hz, 1H, $\underline{CH}SO$), 7.03 (dt, J=1.6 and 8.2 Hz, 1H, H-4 C_6H_4), 6.67 (dd, J=1.3 and 8.2 Hz, 1H, H-3 C_6H_4), 6.54 (ddd, J=1.3, 7.5 and 8.2 Hz, 1H, H-5 C_6H_4), 5.42 (s, broad, 2H, NH_2), 2.65 (s, 3H, CH_3). ^{13}C-δ(DMSO-d_6) 147.2 (C-2), 132.2 (C-6), 131.6 ($\underline{CH}C_6H_4$), 130.3 ($\underline{CH}SO$), 127.4 (C-4), 117.7 (C-1), 116.4 (C-5), 116.3 (C-3), 40.5 (CH_3).

(E)-Aminostyryl methyl sulfone (13). It was obtained from **6** or **11** by treatment with potassium carbonate. Crystallized from cyclohexane/ethanol, mp 128-30°, yield 90 %. (Found: C 54.72, H 5.53, N 7.29, S 16.22. $C_9H_{11}NO_2S$ requires C 54.80, H 5.62, N 7.10, S 16.25). ν_{max}(KBr) 3460, 3400, 1660, 1305, 1130, 980, 755 cm^{-1}. m/z 197 M^+ (34), 182 (1), 118 (95), 117 (100), 91 (37), 84 (17), 65 (14), 51 (13). ^{1}H-δ($CDCl_3$) 7.75 (d, J=15.2 Hz, 1H, $\underline{CH}C_6H_4$), 7.33 (dd, J=1.6 and 7.8 Hz, 1H, H-6 C_6H_4), 7.24 (dt, J=1.6 and 8.1 Hz, 1H, H-4 C_6H_4), 6.85 (d, J=15.2 Hz, 1H, $\underline{CH}SO_2$), 6.76 (m, 2H, H-3 and H-5 C_6H_4), 3.71 (s, broad, 2H, NH_2), 3.04 (s, 3H, CH_3). ^{13}C-δ($CDCl_3$) 145.9 (C-2), 139.6 ($\underline{CH}C_6H_4$), 132.4 (C-6), 128.7 ($\underline{CH}SO_2$), 126.0 (C-4), 119.4 (C-5), 117.7 (C-1), 117.4 (C-3), 43.4 (CH_3).

4-Methyl-1,4H-3,1-benzoxazin-2-one (16). A solution of 0.2 g (0.96 mmol) of **14** was treated in 15 ml of THF with 0.02 g (0.53 mmol) of sodium borohydride. After 2 hours at room temperature the solution was diluted with 2 ml of water and extracted with methylene chloride. A mixture 2/1 of **15** and **16** was isolated. In order to complete the conversion the mixture

was treated with potassium carbonate following the general procedure described above. Crystallized from cyclohexane, yield 80%, mp 108-9°. (Found: C 66.15, H 5.80, N 8.80. $C_9H_9NO_2$ requires C 66.25, H 5.56, N 8.80). ν_{max}(nujol) 3100, 1700, 1590, 1490, 1280, 1265, 1050, 750 cm^{-1}. m/z 163 M^+ (53), 148 (22), 118 (100), 104 (10), 91 (32), 77 (10), 65 (13). ^1H-$\delta(CDCl_3)$ 9.62 (s, broad, 1H, NH), 7.31 (m, 2H, H-6 and H-8), 7.15 (t, J=7.7 Hz, 1H, H-7), 6.93 (d, J=7.5 Hz, 1H, H-5), 5.52 (q, J=6.6 Hz, 1H, H-4), 1.70 (d, J=6.6 Hz, 3H, CH_3). ^{13}C- $\delta(CDCl_3)$ 153.6 (CO), 135.0 (C-8a), 129.0 (C-7), 123.6 (C-5), 123.3 (C-6), 122.6 (C-4a), 114.3 (C-8), 75.9 (C-4), 20.3 (CH_3).

N-[2-(2-Bromo-1-hydroxyethyl)phenyl]ethyl carbamate (**18**). Prepared quantitatively from **17**[1] by reduction with sodium borohydride in THF following the same procedure described for **15**. ν_{max}(film) 3350, 2970, 1710, 1590, 1520, 1230, 1050, 760 cm^{-1}. m/z 289 M^++2 (12), 287 M^+ (11), 207 (21), 162 (100), 148 (55), 136 (25), 118 (45), 106 (18), 94 (26), 75 (40). ^1H-$\delta(CDCl_3)$ 8.33 (s, broad, 1H, NH), 7.92 (dd, J=1.1 and 8.8 Hz, 1H, H-6 C_6H_4), 7.29 (ddd, J=1.7, 7.1 and 8.8 Hz, 1H, H-5 C_6H_4), 7.11 (dt, J=1.7 and 7.6 Hz, 1H, H-3 C_6H_4), 7.01 (ddd, J=1.1, 7.1 and 7.6 Hz, 1H, H-4 C_6H_4), 4.92 (m, 1H, CH-O), 4.19 (q, J=7.0 Hz, 2H, CH_2O), 4.08 (d, J=3.2, 1H, OH), 3.62 (m, 2H, CH_2-Br), 1.30 (t, J=7.0 Hz, 3H, CH_3). ^{13}C-$\delta(CDCl_3)$ 154.2 (CO), 136.0 (C-1), 128.9 (C-2), 128.6 (C-5), 127.6 (C-3), 123.4 (C-4), 121.8 (C-6), 73.8 (CH-O), 61.0 (CH_2-O), 36.6 (CH_2-Br), 14.1 (CH_3).

2-Ethoxycarbonylaminostyrene oxide (**19**). To a solution of 0.5 g (1.73 mmol) of **18** in 20 ml of methylene chloride a catalytic amount of TBAI and 6.9 g of 1% aqueous sodium hydroxide were added. After 45 minutes the phases were separated and the organic one dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography using methylene chloride/methanol (20/1) as eluent. Yield 88%. (Found: C 63.65, H 6.25, N 6.44, $C_{11}H_{13}NO_3$ requires C 63.76, H 6.32, N 6.76). ν_{max}(film) 2980, 1710, 1595, 1525, 1450, 1310, 1225, 1060, 880, 765 cm^{-1}. m/z 207 M^+ (100), 179 (25), 148 (65), 134 (79), 120 (34), 117 (63), 106 (72), 91 (25), 77 (53), 65 (15). ^1H-$\delta(CDCl_3)$ 7.87 (d, J=8.8 Hz, 1H, H-3 C_6H_4), 7.64 (s, broad, 1H, NH), 7.25 (m, 2H, H-4 and H-6 C_6H_4), 7.06 (ddd, J=1.1, 7.1 and 7.6 Hz, 1H, H-5 C_6H_4), 4.20 (q, J=7.0 Hz, 2H, CH_2O), 3.98 (m, 1H, CH-O), 3.00 (m, 2H, CH_2-O), 1.31 (t, J=7.0 Hz, 3H, CH_3). ^{13}C-$\delta(CDCl_3)$ 153.9 (CO), 136.5 (C-2), 128.5 (C-1 and C-4), 126.9 (C-6), 123.6 (C-5), 119.6 (C-3), 61.1 (CH_2-O), 51.7 (CH), 48.6 ($\underline{CH_2}$-C), 14.3 (CH_3).

N-Ethoxycarbonyl-3-hydroxyindoline (**20**). Obtained from **18** by treatment with sodium hydride. Crystallized from hexane, mp 82-4°, yield 90%. (Found: C 63.58, H 6.23, N 6.72. $C_{11}H_{13}NO_3$ requires C 63.76, H 6.32, N 6.76). ν_{max}(nujol) 3470, 3441, 1679, 1599, 1316, 1156, 1049, 1012, 766, 751 cm^{-1}. m/z 207 M^+ (100), 189 (40), 179 (12), 134 (49), 130 (42), 117 (86), 106 (76), 89 (30), 77 (52), 63 (18), 51 (21). ^1H-$\delta(CDCl_3)$ 7.80 (m, 1H, H-7), 7.35 (m, 2H, H-4 and H-6), 7.05 (dt, J=1.0 and 6.7 Hz, 1H, H-5 Ph), 5.25 (m, 1H, CH-O), 4.00 (m, 2H, CH_2-N), 4.21 (q, J=7.0 Hz, 2H, CH_2O), 1.33 (t, J=7.0 Hz, 3H, CH_3). ^{13}C-$\delta(CDCl_3)$ 153.0 (CO), 132.2 (C-7a), 129.8 (C-6), 125.2 (C-4), 122.8 (C-5), 120.8 (C-3a), 114.9 (C-7), 69.2 (C-3), 61.5 (CH_2-O), 56.6 (C-2), 14.4 (CH_3).

N-Ethoxycarbonyl-2-hydroxyindoline (**21**). Obtained from **19** by treatment with sodium hydride in THF. Crystallized from hexane. Yield 88%. Physical

constants and spectral data are in fully agreement with those reported in the literature.[7]

N-Ethoxycarbonylindol (23). A solution of **20** or **21** in toluene was refluxed with a catalytic amount of p-toluenesulfonic acid in toluene for 30 minutes. The mixture was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by chromatography using methylene chloride/methanol (40/1) as eluent. Yield 90%. Its spectral data are fully identical with that reported in the literature.[9]

N-Ethoxycarbonyl-3-indolinone (24). Obtained from **17** by treatment with sodium hydride. Crystallized from hexane/acetone. Yield 88%, mp 73-5°. (Found: C, 64.28; H, 5.36; N, 7.00. $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.82). ν_{max}(KBr) 3280, 3000, 1710, 1600, 1530, 1470, 1230, 1060, 750 cm^{-1}. m/z 205 M^+ (100), 190 (0.4), 177 (6), 160 (7), 133 (33), 105 (74), 91 (10), 77 (35), 51 (85). ^{1}H-$\delta(CDCl_3)$ 8.23 (m, 1H, H-4), 7.75 (m, 2H, H-5 and H-7), 7.15 (dt, J=1.0 and 7.8 Hz, 1H, H-6 C_6H_4), 4.35 (q, J=7.2 Hz, 2H, CH_2-O), 4.23 (s, 2H, CH_2-CO) and 1.36 (t, J=7.2 Hz, 3H, CH_3). ^{13}C-$\delta(CDCl_3)$ 195.6 (CO), 153.5 (COO), 140.5 (C-7a), 137.0 (C-5), 124.0 (C-3a), 123.7 (C-4), 123.1 (C-6), 116.6 (C-7), 62.4 (CH_2-O), 55.1 (C-2), 14.4 (CH_3).

N-[2-(2-Cyano-1-hydroxyethyl)phenyl]ethyl carbamate (25). To a suspension of 0.76 mmol of sodium cyanide in 3 ml of anhydrous DMF 0.76 mmol of **19** in 3 ml of DMF was added. After 17 hours the mixture was quenched with 0.5 ml of water and the organic material extracted with methylene chloride. The organic layer was washed with water then dried over sodium sulfate. The solvent was removed under reduced pressure aided with additions of small portions of toluene and the residue was chromatographied using methylene chloride/methanol (20/1) as eluent yielding 113 mg (64%) of **25** as an oil. (Found: C 61.48, H 6.05, N 11.85. $C_{12}H_{14}N_2O_3$ requires C 61.53, H 6.02, N 11.96). ν_{max}(film) 3340, 2990, 2220, 1700, 1610, 1600, 1530, 1490, 1410, 1310, 1230, 1060, 760 cm^{-1}. m/z 207 M^+-HCN (59), 189 (10), 144 (49), 134 (20), 117 (100), 106 (48), 90 (25), 77 (24), 63 (10). ^{1}H-$\delta(CDCl_3)$ 8.10 (s, broad, 1H, NH), 7.82 (dd, J=1.0 and 8.6 Hz, 1H, H-6 C_6H_4), 7.32 (ddd, J=1.6, 7.3 and 8.6 Hz, 1H, H-5 C_6H_4), 7.08 (m, 2H, H-3 and H-4 C_6H_4), 5.05 (m, 1H, CH-O), 4.55 (s, broad, 1H, OH), 4.18 (q, J=7.2 Hz, 2H, and CH_2O), 2.82 (m, 2H, CH_2-CN), 1.30 (t, J=7.2 Hz, 3H, CH_3). ^{13}C-$\delta(CDCl_3)$ 154.3 (CO), 136.2 (C-1), 129.9 (C-2), 129.4 (C-5), 127.2 (C-3), 124.2 (C-4), 122.9 (CN), 122.6 (C-6), 69.8 (CH-O), 61.4 (CH_2-O), 25.5 (CH_2-CN), 14.4 (CH_3).

2-Aminocinnamonitrile ((E)-27 and (Z)-27). They were obtained from **25** as an equimolecular mixture of Z and E isomers following the general procedure of reaction with potassium carbonate described above. Yield 93%. The treatment of such a mixture with 10% aqueous sodium hydroxide yielded 2-aminoquinoline and the unaltered isomer (E)-**27**. Pure (E)-**27** could be isolated by chromatography using ethyl acetate/hexane (1/1) as eluent, mp 130-2° (Lit[13] 134-5°).

2-Aminoquinoline (28). To a solution of 0.61 mmol of **25** in MeOH 0.9 ml of 1% aqueous sodium hydroxide was added. The mixture was refluxed for 24 hours. After cooling the solution was neutralized with 5% hydrochloric acid and extracted with methylene chloride. It was purified by chromatography using ethyl acetate/hexane (1/1) as eluent. Yield 90%, mp

130-1· (Lit[13] 129-30·). Its spectral data are fully identical with that reported in the literature.

Table 1: ^{1}H-nmr parameters and conformational populations of compounds **5α**, **5β**, **8α** and **8β**.

Com	S[a]	c[b]	Chemical Shifts (δ, ppm) H(1)	H(2)	H(3)	OH	Coup. Constants (Hz) $J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{1,OH}$	Populat. x_A	x_B	x_C
5α	A	1.0	5.47	3.41	2.79	5.59	11.3	2.3	-13.3	3.9	99	0	1
		0.01	5.61	3.58	2.67	4.29	11.0	2.1	-13.8	2.3	97	-3	6
	B	2.0	5.17	3.04	2.87	6.12	10.6	2.8	-12.8	4.6	91	5	4
5β	A	1.0	5.48	3.34	2.97	4.84	9.4	3.4	-13.1	-	77	10	13
		0.1	5.52	3.37	2.95	4.66	9.9	2.7	-13.1	1.5	84	2	13
	A/B[d]	2.0	5.22	3.15	3.11	-	7.7	5.7	-12.9	-	53	36	12
8α	A	0.5	5.96	3.33	3.17	-	11.0	2.3	-13.5	-	95	5	0
	B	2.0	5.73	3.40	3.25	-	11.0	2.6	-13.7	-	94	9	-3
8β	A	0.5	6.02	3.40	3.25	-	6.4	6.3	-13.6	-	37	42	20
	B	2.0	5.80	3.33	3.40	-	7.4	6.0	-13.1	-	48	41	11

[a]Solvent: A $CDCl_3$, B DMSO-d_6. [b]Concentration (%, w/v). [d]A:B (1:1) mixture, in pure DMSO-d_6 **5β** show a deceptively simple spectrum.

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