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MODELS OF FOLATE COENZYMES 13 [1] SYNTHESES OF BENZO[a]QUINOLIZINE AND INDOLO[2,3-a]QUINOLIZINE DERIVATIVES VIA CARBON FRAGMENT TRANSFER FROM FOLATE COENZYME MODELS

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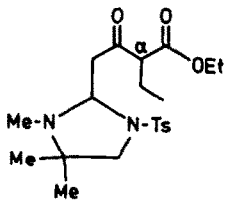
Abstract - Anions of β,β-disubstituted acetyl acetates (2, $CH_2COCR_1R_2COOR_3$, $R_1 = R_2 = Me$, $R_1 = Et$, $R_2 = COOMe$, $R_1 = Et$, $R_2 = SPh$) add to 1-tosyl-3,4,4-trimethyl-Δ^2-imidazolinium iodide (3) to give the corresponding imidazolines (4), which are regarded as models of methylenetetrahydrofolate These models transfer C(2) of the imidazalodine -with its appended carbon fragment- to tryptamine and 2-(3,4-dimethoxybenzene)ethyl amine to yield enaminoketo ester intermediates which can be converted into benzo[a]quinolizine and indolo[2,3-a]quinolizine derivatives, respectively, in two cyclization steps The intermediate derived from transfer of carbon fragment $>CH-CH_2COC(SPh)(Et)COOMe$ to tryptamine exhibits reactions which involve nucleophilic displacement at a sulfur atom of a thio ether bond

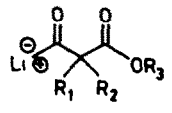
The application of suitable designed imidazolidines in the syntheses of a number of heterocyclic systems has been recently reported from this laboratory [3a-c] This general approach has been termed as "carbon-fragment transfer methodology", in view of the analogy of the crucial step of the reaction sequence to the one carbon unit transfer by coenzymes of tetrahydrofolate [4] The imidazolidines themselves have therefore been regarded as models of N^5,N^{10}-methylenetetrahydrofolate [5] We present here the convenient synthesis of benzo[a]quinolizine and indolo[2,3-a]quinolizine derivatives via suitable models A preliminary communication on this work has been reported earlier [6]

An appropriate methylenetetrahydrofolate model which can -via carbon-fragment transfer- lead to benzo[a]quinolizine and indolo[2,3-a]quinolizine derivatives, in turn capable of elaboration to a number of isoquinoline and indole alkaloids, is imidazolidine derivative 1 (Scheme A) Although 1 could be readily synthesized[7] and its C(2)-fragment transferred with facility to 3,4-dimethoxybenzeneethyl amine and tryptamine, the resulting enaminoketo ester intermediates (analogous to 6 and 7 Scheme A) could not be efficiently cyclized[7] to the desired benzoquinoline and indoloquinolizine derivatives It was felt that the enolizable proton of the β-keto ester moiety in the intermediates, derived from 1, interfered with the base-catalyzed cyclization step This reasoning suggested (a) a study aimed at confirmation of the proposed role of the enolizable proton and (b) a synthetic strategy in which a blocking group introduced at α-carbon of the model (1) was removed after the sequence of cyclization steps, starting from enaminoketo esters of type 5 In order to test whether α-proton(s) of the aforementioned intermediates inhibited acid/base catalyzed cyclizations, the model 4a was synthesized by addition of salt 3 to anion 2a (LDA/THF, -40°) Workup of the reaction mixture showed (NMR) that product 4a was contaminated by varying amounts of the enaminoketo ester 5a The imidazolidine ring of 4a could, however, be readily opened by treatment with triethylamine (50°, $CHCl_3$, 2h) to yield crystalline 5a in quantitative yield Reaction of 5a with 3,4-dimethoxybenzeneethylamine and tryptamine, in presence of acetic acid, resulted in a smooth exchange of the amine moiety of 5a, to give 6 and 7a, respectively

Orientation experiments aimed at accomplishment of the two sequential cyclization steps, starting



1



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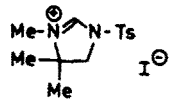

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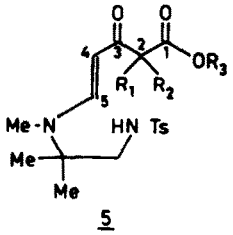

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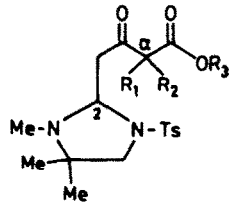
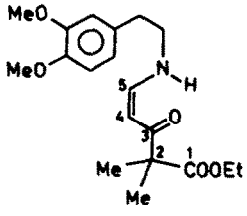


4

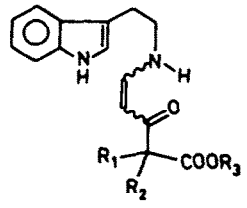
a $R_1 = R_2 = Me$, $R_3 = Et$

b $R_1 = Et$ $R_2 = COOMe$ $R_3 = Me$

c $R_1 = Et$, $R_2 = SPh$ $R_3 = Me$



6



7a $R_1 = R_2 = Me$ $R_3 = Et$

7b $R_1 = Me$ $R_2 = COOMe$, $R_3 = Me$

7c $R_1 = Et$ $R_2 = SPh$, $R_3 = Me$

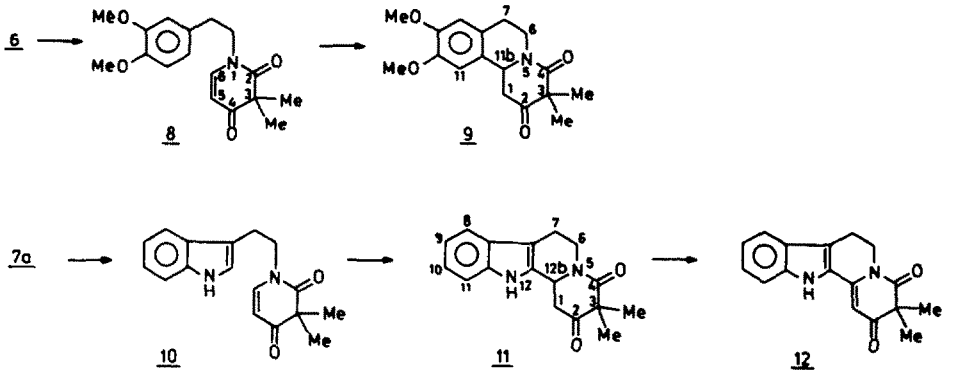
Scheme A

from 6 and 7a, pointed to the advantage of the sequence in which initial ring closure involved the formation of the lactam moiety The reactions 6a → 8 and 7a → 10, proceded in high yields when the starting esters were allowed to react with NaH in THF (Scheme B) The pyridones 8 and 10 underwent smooth acid catalyzed cyclizations to tri- and tetracyclic heterocycles 9 and 11, respectively The indoloquinolizine 11 is highly prone to (air) oxidation to the dehydro product 12 Thus, during attempted purification or when solutions of the compound are allowed to stand for long periods of time 11 is converted into 12 However, crystalline 11 is a stable compound when kept at 0°, under nitrogen

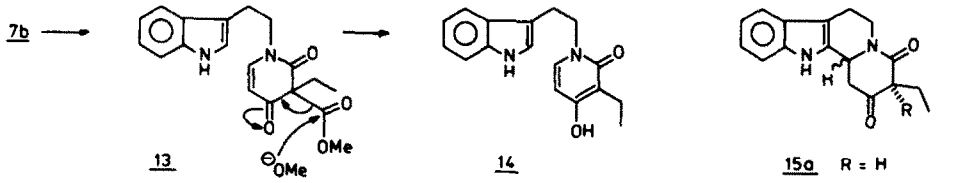
Having established that the presence of an enolizable proton in the enaminoketo ester, (derived from reaction of 1 with arylethylamine or tryptamine) prevented the facile cyclizations leading to benzoquinolizine and indoloquinolizine derivatives, attention was directed to introduction of groups, in the model, which could be later removed at a convenient point in the synthetic scheme In the first attempt towards this objective, model 4b was synthesized by reaction of anion 2b[8] with salt 3 Transfer of the carbon-fragment of 4b, via 5b, to tryptamine yielded the expected enamino ketone 7b Interestingly, whereas 7a was a single isomer possessing the Z geometry, 7b consisted of a mixture of Z (70%) and E (30%) geometric isomers (vide experimental) The base-catalyzed cyclization of the amino ester moiety was then examined Treatment with NaH in tetrahydrofuran, at 0 °C resulted in the formation of pyridone 14, in which the second ester group had been lost In contrast, when the reaction was carried out at -40 °C, the formation of ester 13 could be demonstrated Furthermore, it was observed that at -15 °C, the reaction mixture contained 14 as the sole reaction product These results suggest that while at -40 °C, cyclization occurs in the expected manner, to give product 13, the latter is unstable with respect to a nucleophilic attack at the ester carbonyl function, by the methoxide ion generated in the reaction The subsequent loss of the ester moiety of 13, to yield 14, is obviously a consequence of the facile expulsion of the highly stabilized β-keto amide anion Although 14 could be conveniently prepared by the abovementioned sequence of reactions, the inability to convert 14 to 15a, due to the presence of the highly acidic proton, led us to abandon this approach where the enolizable proton was exchanged for an ester moiety It should be mentioned that although 13 could be directly cyclized to 15b (HCl/Et_2O, C_6H_6), the availibility of 13 was so restricted as to make the method of little use for practical purposes

In a second attempt to introduce a removable group at the α-position of the β-keto ester system 4, attention was directed to model 4c It was visualized that the thiophenyl group could, after oxidation,[9] be subjected to a base-catalyzed elimination reaction Ester 2c was readily obtained in two steps, from methyl 2-bromobutyrate (16 → 17 → 2c, Scheme D) The anion of 2c reacted with 3 to yield 5c (via 4c) which allowed the transfer of C(2) -with its appended carbon fragment- to tryptamine, to form enaminoketo ester 7c However, when attempts were made to cyclize 7c, under influence of base (NaH), two products were obtained in 80% yield One of the products was identical to pyridone 14, while the second component has been assigned structure 18 (Scheme E) This assignment is based upon spectral data of the compound (vide experimental) In particular, the mass spectrum was specially informative A comparison of the mass spectra of 14 and 18 shows that both compounds exhibit an analogous fragmentation pattern with significant peaks which differ by a constant mass displacement of 108 Thus, the peaks at 252, 251 and 238 in the spectrum of 18 parallel the peaks at 144, 143 and 130 in that of 14 The lastmentioned fragments are typical of 3-indole derivatives bearing the 4--hydroxy-2-pyridone moiety[10] and can be attributed to ions a, b and c (R = H, Scheme F) By analogy, the ions of 108 mass units higher, arising from 18, can be assigned to ions a, b and c (R = SPh)

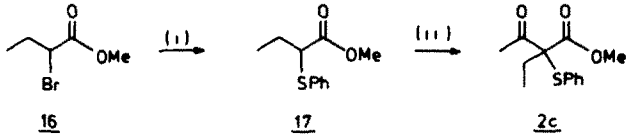
The formation of 14 and 18, upon treatment of 7c with NaH, deserves comment It is evident that in both products the -SPh group has migrated from its original position to either an external acceptor or the indole nitrogen This requires an initial sulphur-carbon bond fission of the thio ether moiety under basic conditions Although cleavage of thio ethers is generally subject to electrophilic catalysis,[11] nucleophilic substitution at dicoordinated sulfur, especially involving displacement of electronegative groups (halogens, O-, S-, N) is well documented [12] In contrast, cases of displacement of a carbon fragment are scarce and limited to examples of stabilized carbanions [13] Bearing these results in mind a mechanistic pathway is suggested for the formation of 14 and 18, in Scheme E Removal of a proton from 7c can result in an equilibrium mixture of two anions, namely 19



Scheme B

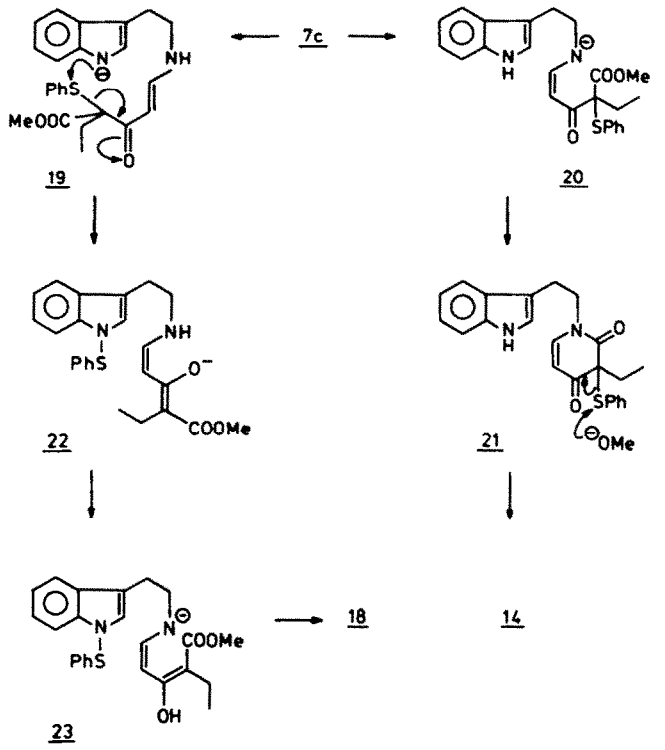


Scheme C

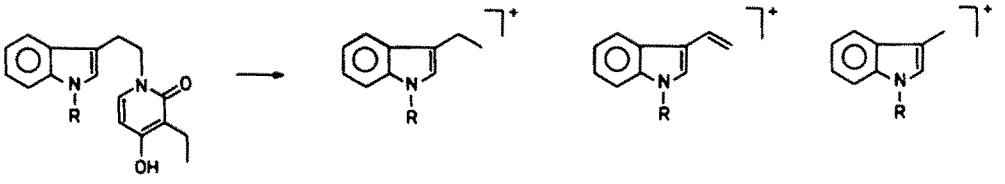


(i) PhSNa / THF (ii) LDA CH_3COCl THF

Scheme D



Scheme E



14	R=H	282	144	143	130
18	R=SPh	390	252	251	238

Scheme F

and 20 It should be emphasized at this point that while the geometry about the double bonds of 7a-c is dependent upon steric factors and hydrogen bonding, the Z and the E isomers are, in principle, interconvertible A similar lack of geometrical integrity of the double bonds in the enamide chains in 19, 20, 22 and 23 is also valid According to the proposed mechanism, anion 20 cyclized to the unsaturated keto lactam 21, which, under the reaction conditions, is not stable with respect to a nucleophilic attack by the generated methoxide anion on the sulphur atom of the thio ether moiety It will be appreciated that the facility of this reaction finds its origin in the high stability of the departing pyridine-2,4-dione anion For the formation of 18, an intramolecular transfer of the SPh group from C to N_1 (19 → 22), via a nucleophilic substitution at the sulfur in 19, is visualized as the initial step The released carbanion moiety in 22 is, once again, a highly stabilized species Conversion of 22 to 18 involves an initial N → O proton shift, followed by cyclization of the resulting anion 23, via an ester aminolysis step

The crucial step in the aforementioned mechanistic scheme, for the formation of 14 and 18, comprises displacement of a resonance stabilized anion by nucleophilic attack on divalently bonded sulfur In support of the mechanisms suggested in Scheme E, it was found that treatment of 7c with sodium methoxide resulted in the formation of both 14 and 18 as the main products Development of synthetic strategy which makes use of other removable groups is currently in progress

EXPERIMENTAL

All mps are uncorrected IR spectra were recorded on a Perkin-Elmer 257 spectrometer The absorptions are given in cm^{-1} PMR spectra were run on a Varian Associates Model A-60-D and XL-100 or Bruker WM 250 instruments, using TMS as an internal standard Mass spectra were obtained with a Varian Matt-711 spectrometer Analyses were carried out at the Microanalytical Laboratory, Department of Physical-Organic and Analytical Chemistry, Organic Chemistry Institute, TNO, Zeist, The Netherlands THF was distilled from $LiAlH_4$ before use

Methyl 2-ethyl-2-(phenylthio)acetate 2c
To a solution of 10 mmol LDA in 100 ml THF was added 10 mmol 17 (2 10 g) dissolved in 5 ml THF at -78 °C under nitrogen After 15 min, 2 5 eq CH_3COCl was added to the mixture which was distilled before use After stirring for 1 hr at -40 °C a concentrated $NaHCO_3$ solution was added to the reaction mixture The mixture was extracted with ether, the organic layer washed with $NaHCO_3$, followed by NaCl and then dried over $MgSO_4$ Evaporation of the solvent, chromatography on SiO_2 with EtOAc/hexane (1 6) followed by bulb to bulb distillation gave a colourless oil (160 °C/0 002 mm) 2c Yield 1 91 g (72%) IR($CHCl_3$) 1763 (w), 1735 (w), 1722 (m), 1709 (s), 688 (m) PMR($CDCl_3$, 60 MHz) 0 98 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 2 10-1 65 (m, 2H, $\underline{CH_2}CH_3$), 2 30 (s, 3H, $CO\underline{CH_3}$), 3 74 (s, 3H, $COO\underline{CH_3}$), 7 50-7 20 (m, 5H, S-ArH), FD (m/e) 252 (M^+)

Ethyl-4-[2-(1-tosyl-3,4,4-trimethyl)imidazolidinyl]-2,2-dimethyl-3-oxo-butanoate (4a) and Ethyl (E)-5-[2-(tosylamino-1,1-dimethyl)ethyl methyl]amino-2,2-dimethyl-3-oxo-4-pentenoate (5a)
1 01 g of diisopropyl amine (10 mmol, 1 42 ml) was dissolved in 150 ml of dry THF under nitrogen At -78 °C 10 mmol of a soln of n-butyllithium in hexane was added to the mixture After 10 min 1 58 g (10 mmol) of 2a, dissolved in 2 ml THF, was added to the mixture After stirring for another 10 min at -78 °C 3 94 g of 3 (10 mmol) was added while the mixture was vigorously stirred The mixture was kept at -40 °C for one hour Subsequently, the reaction mixture was allowed to reach room temperature (2 hr) The reaction mixture was concentrated under reduced pressure The residue was filtered through a column filled with silica gel using EtOAc (ethylacetate) as the eluent Concentration of the filtrate yielded an oil which contained unreacted 2a, the product 4a and a large amount of ring-opened product 5a 4a was recognized in the mixture by some characteristic signals in the PMR($CDCl_3$) spectrum 0 25 (1s, 3H, NC(CH_3)), 2 05 (s, 3H, N-CH_3), 2 42 (s, 3H, TOS CH_3) Isolation from this mixture of 4a was not possible When the mixture was boiled in $CHCl_3$ containing triethylamine (1%) 4a could be readily opened to the more polar compound 5a After 2 hr the mixture was concerted under reduced pressure Recrystallization from EtOH gave 5a as white crystals 5a Yield 2 8 g (66%), mp 130-132 °C (from EtOH) IR($CHCl_3$) 3400-3300 (w), 1716 (s), 1645 (s), 1550 (vs), 1330 (m), 1160 (s) PMR($CDCl_3$, 100 MHz) 1 25 (t, J = 7 Hz, 3H, O-$CH_2\underline{CH_3}$), 1 32 (s, 6H, NC($\underline{CH_3}$)$_2$), 1 38 (s, 6H, $(CH_3)_2$C-C=O), 2 45 (s, 3H, TOS CH_3), 2 73 (s, 3H N-CH_3), 2 96 (d, J = 7 Hz, 2H, $\underline{CH_2}$-NH), 4 17 (q, J = 7 Hz, 2H, O-$\underline{CH_2}CH_3$), 5 09 (d, J = 8 Hz, 2H, TOS C^{6}H and TOS C^{2}H), 7 76 (d, J = 8 Hz, 2H, TOS C^{2}H and TOS C^{6}H), 7 92 (d, J = 12 Hz, 1H, C^{7}H) FD (m/e) 424 (M^+) Found C, 59 50, H, 7 50, N, 6 50 Calc for $C_{21}H_{32}N_2S_1O_5$, C, 59 43, H, 7 54, N, 6 60

Methyl (E)-5-[2-(tosylamino-1,1-dimethyl)ethyl methyl]amino-2-ethyl-2-(methoxycarbonyl)-3-oxo-4--pentenoate (5b)
To a solution of 150 ml THF containing 10 mmol LDA (lithiumdiisopropylamine) was added 2 02 g (10 mmol) of 2b dissolved in 2 ml THF at -78 °C under nitrogen After stirring for 10 min at -78 °C 3 94 g (10 mmol) of 3 was added while the mixture was vigorously stirred The temperature was kept at -70 °C for at least 2 hr After this, the reaction mixture was allowed to reach room temperature (2 hr) After evaporation of the solvent under reduced pressure and chromatography on silica gel using ETOAc EtOAc/hexaan (1 1) as the eluent, 5b could be obtained as white crystals after recrystallization from EtOAc The yield depended on the temperature after the addition of the salt (3) Higher temperature (-40 °C) gave a much lower yield of 5b (13%) 5b Yield 1 68 g (36%), mp 172-173 °C (from EtOAc) IR($CHCl_3$) 3400-3300 (w), 1730 (s), 1648 (s), 1600 (w), 1550 (vs), 1160 (s) PMR($CDCl_3$)

0 96 (t, J = 7 4 Hz, 3H, C^2-$CH_2\underline{CH_3}$), 1 29 (s, 6H, $NC(\underline{CH_3})_2$), 2 16 (q, J = 7 4 Hz, 2H, C^2-$\underline{CH_2}CH_3$), 2 41 (s, 3H, TOS CH_3), 2.69 (s, 3H, N-CH_3), 2 94 (q, J = 6.4 Hz, 2H, $\underline{CH_2}NH$), 3 74 (s, 6H, $\underline{COOCH_3}$), 5 11-5 06 (m, 1H, NH), 5 25 (d, J = 12 2 Hz, 1H, C^6H), 7.29 (d, J = 8.3 Hz, TOS C^3H and TOS C^5H), 7.69 (d, J = 8 3 Hz, 2H, TOS C^2H and TOS C^6H), 7.88 (d, J = 12.2 Hz, 1H, C^5H). MS Found 468.1917 Calc for $C_{22}H_{32}N_2S_1O_7$ 468 1930.

Methyl (E)-5-[2-(tosyl)amino-1,1-dimethyl)ethyl]methyl amino-2-ethyl-2-(phenylthio)-3-oxo-4--pentenoate (5c)

To a solution of 6.4 mmol LDA in THF (-78 °C, nitrogen) was added 1612 mg of 2c (6.4 mmol) in 10 ml THF After 15 min 2.52 g of 3 (6 4 mmol) was added to the reaction mixture The reaction mixture was rigorously stirred for 1 hr at -40 °C After stirring for another hr at room temperature the reaction mixture was concentrated under reduced pressure The residue was filtered through a short column (SO_2/EtOAc). Isolation from this resulting mixture of 4c was not possible. Ring-opened product 5c was crystallized from this mixture with EtOAc (500 mg, 0 96 mmol) The resulting mother layer was allowed to stand for 24 hr at 20 °C in $CHCl_3$. Chromatography on SiO_2 with CH_2Cl_2/EtOAc (3 1) gave an additional 1170 mg (2 25 mmol) of 5c after crystallization from EtOAc The first fraction which was collected from this chromatography on SiO_2 was a mixture of starting ester 2c and 17 (15% and 10%, respectively) 2c has a tendency to fragment to the corresponding ketene and to the anion of methyl-2-(phenylthio)butyrate (17) [19] 5c Yield 1670 mg (50 3%), mp 203-205 °C (from EtOAc). IR($CHCl_3$) 3400-3300 (w), 3240-3100 (w), 1725 (s), 1640 (s), 1560-1550 (vs), 1160 (s), 1372 (m), 1330 (m) PMR($CDCl_3$, 250 MHz) 0.99 (t, J = 7 3 Hz, 3H, C^2-$CH_2\underline{CH_3}$), 2.39 (s, 3H, TOS CH_3), 2 71 (s, 3H, N-CH_3), 2 90 (d, J = 6 8 Hz, 2H, $\underline{CH_2}NH$ TOS), 3 70 (s, 3H, $\underline{COOCH_3}$), 5 32 (d, J = 12 1 Hz, 1H, C^6H), 5 83 (t, J = 6 8 Hz, 1H, NH), 7 33-7 24 (m, 5H, TOS C^3H, TOS C^5H and SAr (C^3H, C^4H, C^5H), 7 44-7 40 (m, 2H, SAr C^6H, SAr C^2H), 7 70 (d, J = 8.2 Hz, 2H, TOS C^2H and TOS C^6H), 7 91 (d, J = 12 1 Hz, 1H, C^5H) EI (70 eV) no M^+. FD 518 Calc for $C_{26}H_{34}N_2S_2O_5$ 518

Ethyl(Z)-5-(3,4-dimethoxyphenethylamino)-2,2-dimethyl-3-oxo-4-pentenoate (6) [15]

A mixture of 5a (1 mmol, 424 mg), 3,4-dimethoxyphenylethylamine (226 55 mg, 1 25 mmol), acetonitrile (5 ml, dry) and acetic acid (0.5 ml, dry) was refluxed for 2-2 5 hr (under nitrogen atmosphere) The reaction was monitored on silica gel using EtOAc/CH_2Cl_2 (1 2! as eluent The mixture was concentrated under reduced pressure, using toluene to remove the acetic acid. The resulting red oil was brought on silica gel using EtOAc/CH_2Cl_2 (1 3) as the eluent After concentration under reduced pressure, the eneaminoketo ester was obtained as a yellow oil 6 Yield 279 mg (80%) IR($CHCl_3$) [16,17] 1718 (s), 1635 (s), 1560 (s), 1510 (m), 3300-3100 (w) PMR($CDCl_3$, 100 MHz) 1 24 (t, J = 7 Hz, 3H, $OCH_2\underline{CH_3}$), 1 38 (s, 6H, $C^2(CH_3)_2$), 2 79 (t, J = 6 5 Hz, 2H, $\underline{CH_2}CH_2NH$), 3 50-3 30 (dt, J = 6 5 Hz, J = 6 6 Hz, 2H. $CH_2\underline{CH_2}NH$), 3.88 (s, 6H, 2xOCH_3), 4 17 (q, J = 7 Hz, 2H, $O\underline{CH_2}CH_3$), 4 95 (d, J = 7 5 Hz, 1H, C^6H), 6.60 (dd, J = 12.0 Hz, J = 7 5 Hz, 1H, C^5H), (after quenching with D_2O this dd gives a d centered at 6 60), 6 86-6 66 (m, 3H, Ar), 10 0-9 65 (bs, 1H, N-H) MS Found 349 1906 Calc for $C_{19}H_{27}N_1O_5$ 349 1889

Ethyl(Z)-5-[2-(3-indolyl)-ethylamino]-2,2-dimethyl-3-oxo-4-pentenoate (7a)

A mixture of 5a (1 mmol, 424 mg), tryptamine (200 mg, 1 25 mmol) (mw 160.22, mp 114-119 °C), acetonitrile (5 ml, dry) and acetic acid (0 5 ml, dry) was refluxed for 2-2.5 hr. After work-up of the reaction mixture (which was identical to that of 6), a yellow oil was obtained 7a Yield 262 4 mg (80%) IR($CHCl_3$) 3480 (s), 3400-3200 (w), 1720 (s), 1638 (s), 1562 (s), 1485 (w), 1380 (m), 1360 (m). PMR($CDCl_3$, 100 MHz) 1.24 (t, J = 7 Hz, 3H, $OCH_2\underline{CH_3}$), 1 39 (s, 6H, $C^2(CH_3)_2$), 2 79 (t, J = 6 5 Hz, 2H, $\underline{CH_2}$-CH_2-NH), 3 60-3.46 (dt, J = 6.5 Hz, J = 6 5 Hz, 2H, CH_2-$\underline{CH_2}$-NH), 4 16 (q, J = 7 Hz, 2H, O-$\underline{CH_2}$-CH_3), 4 94 (d, J = 7 5 Hz, 1H, C^6H), 6 64 (dd, J = 7 5 Hz, J = 12.0 Hz, 1H, C^5H), 6 96 (d, J = 2 2 Hz, 1H, indole C^2H), 7 60-7 10 (m, 4H, indole ArH), 8 45-8 30 (bs, 1H, indole NH), 10-9 60 (bs, 1H, NH) MS Found 328 1794 Calc for $C_{19}H_{24}N_2O_3$ 328 1786

Methyl (Z/E)-5[2-(3-indolyl)-ethylamino]-2-ethyl-2-(methoxycarbonyl)-3-oxo-4-pentenoate (7b)

A mixture of 5b (1 mmol, 468 mg), 200 mg tryptamine (1.25 mmol), acetonitrile (5 ml, dry) and acetic acid (0 5 ml, dry) was kept at 60 °C during 72 hr under nitrogen until all the starting material had disappeared (TLC SiO_2, EA/CH_2Cl_2 1 5) Evaporation of the solvent and chromatography on SiO_2 using EtOAc/CH_2Cl_2 (1 5) as the eluent afforded a yellow oil concisting of 3 products, Z and E isomers of the eneamino-keto ester 7b and a small amount of the piperidine-2,4-dione (13). FD of the mixture gave m/e 372 (7b) and m/e 340 (13) According to NMR the mixture consisted of 72 6% Z, 20.4% E and 7% of compound 13 Yield 82% based on 5b. When 4 5 mmol tryptamine was used instead of 1 25 mmol the reaction was completed within 3 hr (75 °C). After identical work-up, the yield was 70% The mixture consisted of the Z and E isomers only (Z/E, 7 3) 7b Yield 260 4 mg (70%) Yellow oil IR($CHCl_3$) 3480 (m), 3599-3200 (w), 1730 (s), 1638 (s), 1570-1555 (s), 1485 (m) PMR(CD_3CN, 259 MHz 0 87 (t, J = 7 4 Hz, 3H, C^2-$CH_2\underline{CH_3}$), 2 05 (q, J = 7.4 Hz, 2H, C^2-$\underline{CH_2}CH_3$), 2 94 (t, J = 6 7 Hz, 2H, $\underline{CH_2}$-CH_2-NH), 3.48 (dt, J = 6 7 Hz, J = 6 6 Hz, 2H, CH_2-$\underline{CH_2}$-NH), 6.06-5.90 (bs, 1H, NH(E)), 3 62 (s, 6H, 2x$\underline{COOCH_3}$), 4 96 (d, J = 7 4 Hz, 1H, C^6H(Z)), 5.30 (d, J = 12 6 Hz 1H, C^6H(E)), 6 79 (dd, J = 7 4 Hz, J = 13,3 Hz, 1H, C^5H(Z)), 7 16-6 96 (m, indole C^5H, C^6H, C^7H) + C^5H (E)), 7 35 (d, J = 8 Hz, 1H, indole C^7H), 7 53 (d, J = 7 7 Hz, 1H, indole C^4H), 9 70-9 60 (bs, 1H, NH(Z)), 9 10-9 08 (bs, 1H, indole NH). MS. Found 372 1640 Calc for $C_{20}H_{24}N_2O_5$ 372 1685

Methyl (Z/E)-5[2-(3-indolyl)-ethylamino]-2-ethyl-2-(phenylthio)-3-oxo-4-pentenoate (7c)

A mixture of 5c (259 mg, 0 5 mmol) 100 mg tryptamine (0 625 mmol), acetonitrile (5 ml) and acetic acid (0 5 m) was kept at 70 °C under nitrogen for 71 hr (TLC EtOAc/CH_2Cl_2 1 1) Evaporation of the solvent, chromatography on SiO_2 (EtOAc/CH_2Cl_2 1 3) gave a yellow foam consisting of the Z and E isomers of the eneamino keto ester 7c Yield 183 mg (87%). IR($CHCl_3$) 3480 (m), 3500-3200 (w), 1725 (s), 1639 (vs), 1570-1555 (vs), 1470 (m). PMR(CD_3CN, 250 MHz, Z/E = 7 3) 0 89 (t, J = 7.3 Hz, 3H, $C^2CH_2\underline{CH_3}$), 1 79-1 68 (m, 2H, C^2-$\underline{CH_2}CH_3$), 2 94 (t, J = 6 7 Hz, 2H, $\underline{CH_2}CH_2NH$), 3.49 (dt, J = 6 7 Hz, J = 6 6 Hz, 2H, $CH_2\underline{CH_2}NH$), 3 61 and 3 59 (2xs, 3H, 2x$\underline{COOCH_3}$), (Z and E isomers), 4 96 (d, J = 7 4 Hz, 1H, C^6H(Z)), 5 35 (d, J = 11 7 Hz, 1H C^6H(E), 5 95 (bs, 1H, NH(E)), 6 78 (dd, J = 7 4 Hz, J =

13 3 Hz, 1H, $C^5H(Z)$), 7 38-6 97 (m, all aromatic protons, except for the indole C^4H which is located at 7 55 (d, J = 8 1 Hz, 1H), $C^5H(E)$ could not be recognized in this multiplet), 9 1 (bs, 1H, indole N-H), 9 5 (bs, 1H, NH(Z)) MS. Found 422.1654. Calc for $C_{24}H_{26}N_2O_3S_1$ 422 1664.

3,3-Dimethyl-5,6-dehydro-1-(3,4-dimethoxyphenethyl)pyperidine-2,4-dione (8)[16]
To a suspension of 1 mmol NaH in 10 ml dry THF was added 1 mmol of the eneaminoketo ester (6a, 349 mg) dissolved in 5 ml dry THF The reaction mixture was stirred under nitrogen at 0 °C for 1 hr (TLC EtOAc/$CHCl_3$ 1 3). After all the starting material had disappeared, the reaction mixture was neutralized with concentrated NH_4Cl/H_2O The organic layer was separated and the water layer was extracted with Et_2O The organic layer was washed with $NaHCO_3$ soln and NaCl soln Drying over Na_2SO_4 followed by evaporation of the solvent, yielded a residue which was purified by chromatography (SiO_2, EtOAc/hexane 1·1) 8· Yield 212 mg (70%), yellow oil. IR($CHCl_3$) 1695 (s), 1655 (s), 1629 (s), 1511 (m), 1461 (m), 1381 (m), 1370 (m). PMR(DMSO-d_6, 100 MHz) 1.20 (s, 6H, $C^3(CH_3)_2$), 2.79 (t, J = 7 0 Hz, 2H, Ar-CH_2-CH_2), 3.71 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3 84 (t, J = 7.0 Hz, 2H, CH_2-CH_2-N), 5.36 (d, J = 8.0 Hz, 1H, C^5H), 6.92-6 83 (m, 3H, Ar), 7 53 (d, J = 8.0 Hz, 1H, C^6H). MS Found 303.1489, Calc for $C_{17}H_{21}N_4O_4$ 303 1470. EI (70 eV, m/z (%)). 303 (20.9), 165 (13), 164 (100), 151 (46 7), 82 (29 9), 69 5 (11.5)

9,10-Dimethoxy-3,3-dimethyl-1,2,3,4,7,11b-6H-Benz[a]quinolizine-2,4-dione (9)
Piperidine-2,4-dione 8 (1 mmol, 303 mg) was dissolved in 20 ml freshly distilled EtOH. Nitrogen was bubbled through the solution for 1 hr After this the reaction mixture was cooled to 0 °c and dry HCl was bubbled through the solutioh for 10 min After the vessel had been closed the reaction mixture was kept at 20 °C for 18 hr. After evaporation of the solvent and crystallization from EtOH the product could be isolated as white needled. 9 Yield 210-240 mg (70-80%), mp 168 °C (from EtOH). IR($CHCl_3$) 1725 (s), 1640 (s), 1511 (s), 1465 (m), 1430 (s), 1360 (s) PMR(DMSO d_6, 250 MHz). 1.25, 1 28 (2xs, 6H, $C^3(CH_3)_2$), 2 93-2 67 (m, 4H, C^1H_{ax}, C^6H_{ax}, C^1H_{ax} and C^1H_{eq}), 3 17 (dd, J = 3.6 Hz, J = 15 9 Hz, C^1H_{eq}), 3 75 (s, 6H, 2xOCH$_3$) 4-69-4 62 (m, 1H, C^6H_{eq}), 5 06-5 00 (m, 1H, $C^{11b}H$), 6 78 (s, 1H, C^7H), 6.90 (s, 1H, $C^{11}H$). The results of dR (double resonance) techniques were as follows irradiation of $C^{11b}H$ (5 06-5 00) gives a doublet for C^1H_{eq} centered at δ 3 17 (J = 15 9 Hz), enhancement of the singlet for $C^{11}H$ (loss of allylic coupling) and changes in the multiplet from 2 93-2 67. MS. Found 303 1460 Calc for $C_{17}H_{21}N_1O_4$ 303 1470. EI (70 eV m/e (%)) 303 (100), 302 (45 5), 288 (33.9), 272 (39 9), 191 (66.8), 84 (30 7). Found C, 67 10, H, 6.89, N, 4 60. Calc for $C_{17}H_{21}N_1O_4$ C, 67 32, H, 6.93, N, 4 62

3,3-Dimethyl-5,6-dehydro-1-[2-(3-indolyl)ethyl]-piperidine-2,4-dione (10)
Procedure for the synthesis of 10 was identical to that of 9 The product after column chromatography was crystallized from benzene/Et (60-80) 1) Yield 97 mg ( )%), mp 114-115 °C (white crystals) IR($CHCl_3$) 3480 (m), 1695 (s), 1656 (s), 1628 (s), 1455 (w), 1435 (m), 1380 (m), 1370 (m). PMR(DMSO-d_6, 250 MHz) 1 17 (s, 6H, C^3-CH_3), 2.95 (t, J = 7 3 Hz, 2H, CH_2-CH_2-N), 3 85 (t, J = 7 3 Hz, 2H, CH_2-CH_2-N), 6.95 (t, J = 8 Hz, 1H, indole C^7H), 7 04 (t, J = 8 Hz, 1H, indole C^6H), 7.12 (d, J = 2 2 Hz, 1H, indole C^2H), 7.31 (d, J = 7 9 Hz, 1H, indole C^7H), 7.48 (d, J = 8 3 Hz, 1H, C^4H), 5 28 (d, J = 8 3 Hz 1H, C^5H), 7 54 (d, J = 7 9 Hz, 1H, indole C^4H), 10 82 (s, 1H, indole N-H) MS Found 282 1345 Calc for $C_{17}H_{18}N_2O_2$ 282 1368 EI (70 eV m/e (%)) 282 (12 5), 144 (13.71), 143 (89 1), 130 (100), 103 (9 15), 82 (16 24). Found C, 72.17, H, 6 50, N, 9.81 Calc for $C_{17}H_{18}N_2O_3$: C, 72 34, H, 6.38, N, 9.92.

3,3-Dimethyl-2,4-dioxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (11)
The same procedure was used as for the synthesis of 9 Solvent used for the cyclization was dry benzene After 24 hr at 20 °C the reaction mixture was concentrated under reduced pressure. The resulting brown crystals were brought on a short silica gel column with EA/PE (60-80) as the eluent. After evaporation of the solvent and crystallization from Et_2O or benzene the product could be obtained as white crystals 11 Yield 197 mg (70%), mp 214-215°C (fromEt_2O) IR($CHCl_3$) 3465 (m), 1725 (s), 1645 (s), 1430 (s), 1355 (w). PMR(DMSO-d_6, 250 MHz): 1 28 (s, 3H, C^3CH_3), 1 29 (s, 3H, C^3CH_3), 3.05-2 71 (m, 4H, C^1H_{ax}, C^6H_{ax}, C^1H_{ax} and C^1H_{eq}), 3.27 (dd, J = 3.9 Hz, J = 15 1 Hz, 1H, C^1H_{eq}), 4.94-4.88 (m, 1H, $C^{12b}H$), 5.17-5 13 (m, 1H, C^6H_{eq}), 7.01 (t, J = 7 8 Hz, 1H, C^9H), 7.10 (t, J = 7.9 Hz, 1H, $C^{10}H$), 7 34 (d, J = 7.9 Hz, 1H, $C^{11}H$), 7.46 (d, J = 7.8 Hz, 1H, C^8H), 9.13 (s, 1H, N-H) Results of dR techniques were irradiation of C^6H at δ 7 46 gives a doublet for C^5H at δ 7 01 Irradiation of $C^{12b}H$ gives a doublet at δ 3.27 (J = 15 1 Hz) for C^1H and changes in the multiplet at 3.05-2 71 Homoallylic coupling between $C^{12}H$ and one of the C^1 protons has been proven. MS Found 282 1345. Calc for $C_{17}H_{18}N_2O_2$ 282.1368. EI (70 eV m/e (%)) 282 (100), 281 (23.9), 267 (11.8), 212 (12), 184 (23 1), 183 (14.1), 170 (32.3), 169 (76 6), 156 (64 6), 154 (36.8). Found C, 72.15, H, 6.40, N, 9.80 Calc for $C_{17}H_{18}N_2O_2$ C, 72 34, H, 6.38, N, 0 92.

3,3-Dimethyl-2,3-dioxo-2,3,4,6,7,12-hexahydroindole[2,3-a]quinolizine (12)
Cyclization of the piperidine-2,3-dione 10 in benzene/HCl containing O_2 gives cyclization followed by oxidation to compound 12 in 70% overall yield Pure quinolizine 11 could be oxidized in $CHCl_3$ containing a few percent HCl/Et_2O within one hour in an almost quantitative yield to compound 12: 12 mp 258-260 °C (from EtOAc/hexane, yellow crystals IR($CHCl_3$)· 3400-3150 (m), 1689 (m), 1628 (s), 1604 (vs), 1485 (w), 1430 (m), 1369 (s). PMR(DMSO-d_6, 250 MHz) 1 35 (s, 6H, C^3CH_3), 3.09 (t, J = 6.4 Hz, 2H, C^7H), 4.09-4 05 (m, 2H, C^6H), 6 08 (s, 1H, C^1H), 7 12 (t, J = 7 9 Hz, C^9H), 7 32 (t, J = 8.2 Hz, $C^{10}H$), 7 45 (d, J = 8 2 Hz, $C^{11}H$), 7.67 (d, J = 7.9 Hz, C^8H), 11 75 (s, 1H, N-H) FD 280 (M^+). Found C, 72 80, H, 5.73, N, 9.85. Calc for $C_{17}H_{16}N_2O_2$ C, 72.85, H, 5.71, N, 10.0.

3-Ethyl-3-(methoxycarbonyl)-1-[2-(3-indolyl)ethyl]-5,6-dehydro-piperidine-2,4-dione (13)
To a suspension of 1 mmol NaH in 10 ml dry THF (-40 °C, under nitrogen) was added 1 mmol of the eneaminoketo ester 7b (372 mg) Temperature was kept -40 °C. TLC monitoring was done with SiO_2/EtOAc After 4 hr (all starting material has disappeared), $NH_4Cl/HCl/H_2O$ was added to the reaction mixture at -30 °C. Et_2O extraction followed by treatment of $NaHCO_3$ soln and NaCl soln Drying over

Na_2SO_4 and evaporation of the solvent gave the crude product which was purified on silica gel (EtOAc/hexane 10 1) 13 Yield 272 mg (80%), yellow oil IR($CHCl_3$) 3480 (s), 1764 (s), 1699 (s), 1655 (s), 1622 (s), 1456 (m), 1448 (m), 1424 (m), 1378 (s). PMR(CD_3CN, 250 MHz) 0 70 (t, J = 7 6 Hz, 3H, $C^3CH_2CH_3$), 2 09 (q, J = 7 6 Hz, 2H, $C^3CH_2CH_3$), 3 02 (m, 2H, CH_2CH_2N), 3 60 (s, 3H, $COOCH_3$), 3 94-3 84 (m, 2H, CH_2CH_2N), 5 33 (d, J = 8 4 Hz, 1H, C^2H), 6 99-7 16 (m, 2H, indole C^5H, indole C^6H), 7 14 (d, J = 8 4 Hz, 1H, C^7H), 7 02 (d, J = 1 9 Hz, 1H, indole C^2H), 7 36 (d, J = 7 9 Hz, 1H, indole C^4H), 7 58 (d, J = 7 7 Hz, 1H, indole C^4H), 9 10 (bs, 1H, indole NH) MS Found 340 1441 Calc for $C_{19}H_{20}N_2O_4$ 340 1424

3-Ethyl-4-hydroxy-1-[2-(3-indolyl)ethyl]-2-pyridone (14)
To a suspension of 0 5 mmol NaH in 10 ml dry THF (under nitrogen) was added 0 5 mmol of 7b (186 mg) dissolved in 2 ml THF The reaction mixture was kept at 0 °C for 18 hr (TLC SiO_2/EtOAc) The reaction mixture was neutralized with conc NH_4Cl/H_2O soln, Et_2O extraction followed by NaCl/H_2O washing of the organic layer, drying over Na_2SO_4 and evaporation of the solvent gave the crude product which was purified on SiO_2/EtOAc 14 Yield 112 mg (79%), white crystals from EtOAc, mp 189-191 °C, IR($CHCl_3$) 3600 (w), 3500-3000 (w), 1655 (s), 1645 (s), 1622 (w), 1610 (w), 1562-155 (s), 1468 (s), 1442 (s), 1280 (s), 1135 (m) PMR(CD_3CN + DMSO-d_6, 250 MHz) 0 98 (t, J = 7 4 Hz, 3H, $C^3CH_2CH_3$), 2 44 (q, 2H, J = 7 4 Hz, $C^3CH_2CH_3$), 3 05-2 99 (m, 2H, CH_2CH_2N), 4 05-3 99 (m, 2H, CH_2CH_2N), 5 76 (d, J = 7 4 Hz, C^5H), 6 85 (d, J = 7 4 Hz, 1H, C^6H), 6 96 (d, J = 2 6 Hz, 1H, indole C^2H), 7 24-6 92 (m, 2H, indole C^5H, indole C^6H), 7 31 (d, J = 8 Hz, 1H, indole C^7H), 7 54 (d, J = 7 8 Hz, 1H, indole C^4H), 9 43 (s, 1H, C^3OH), 9 76 (bs, indole NH) 14 PMR(CD_3CN, 250 Mz) 0 99 (t, J = 7 4 Hz, 3H, $C^3CH_2CH_3$), 2 53-2 37 (m, 2H, $C^3CH_2CH_3$), 3 07-3 00 (m, 2H, CH_2CH_2N), 4 07-4 00 (m, 2H, CH_2CH_2N), 5 73 (d, J = 7 4 Hz, 1H, C^2H), 6 87 (d, J = 7 4 Hz, 1H C^6H), 6 90 (d J = 2 4 Hz, 1H, indole C^2H), 6 97 (t, J = 8 Hz, 1H, indole C^5H), 7 07 (t, J = 8 Hz, 1H, indole C^6H), 7 32 (d, J = 8 Hz, 1H, indole C^7H), 7 54 (d, J = 7 6 Hz, 1H, indole C^4H), 8 0-7 2 (bs, 1H, C^3OH), 9 07-9 05 (bs, 1H, indole NH) NOE results in CD_3CN/DMSO irradiation of C^3OH at δ 9 43 gave a positive enhancement for C^4H at δ 5 76 DR (double resonance) results were (∿ CD_3CN) irradiation of C^5H at δ 5 73 gave a singlet at δ 6 87 for C^6H Irradiation of CH_2CH_2N at δ 3 07-3 00 gave a relative enhancement for indole C^2H (Toss of allylic coupling, see also compound 18) MS Found 282 1401 Calc for $C_{17}H_{18}N_2O_2$ 282 1368

3-Ethyl-3-(methoxycarbonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-2,4-dione (15b)
The ester 13 (140 mg, 0 411 mmol) was dissolved in dry benzene (10 ml, distilled from CaH_2) A nitrogen stream was bubbled through the solution for 2 hr After this 2 ml of a concentrated HCl/Et_2O soln was added to the reaction mixture (20 °C) The reaction was monitored with SiO_2 EtOAc/hexane (1 2) After evaporation of the solvent (reaction time 5 5 hr) and chromatography on SiO_2 EtOAc/hexane (1 3) two products were isolated starting material 13 33 mg (0 097 mmol) (23 6%) Product 15b 74 mg (52 9%) [18] White crystals, mp 88-220 °C (diastereomers) IR($CHCl_3$) 3468 (m), 1764 (s), 1729 (s), 1650 (s), 1460 (m), 1438 (s), 1305 (s) PMR($CDCl_3$/one drop of pyridine) [two diastereomers (88 5% 11 5%) chemical shifts of major diastereomer are given], 0 81 (t, J = 7 4 Hz, 3H, $C^3CH_2CH_3$), 2 45-2 22 (m, 2H, $C^3CH_2CH_3$), 3 13-2 80 (m, 4H, C^1H_{ax}, C^6H_{ax}, C^1H_{ax} and C^1H_{eq}), 3 28 (dd, J = 15 1 Hz, J = 3 6 Hz, 1H, C^1H_{eq}), 3 61 (s, 3H, $COOCH_3$), 5 03-4 96 (m, 1H, $C^{12b}H$), 5 24-5 14 (m, 1H, C^6H_{eq}), 7 18-7 06 (m, 2H, C^9H,$C^{10}H$), 7 30-7 24 (m, 1H + $CHCl_3$, $C^{11}H$), 7 51-7 48 (m, 1H, C^8H), 10 27 (s, 1H, $N^{12}H$) Nuclear Overhauser Difference (NOE) experiments were carried out (Bruker WM 250 MHz) Irradiation of $C^{12b}H$ gave a positive enhancement for $N^{12}H$ at δ 10 27 (s), C^1H_{eq} at δ 3 28 (d, J = 15 1 Hz, J = 3 6 Hz), $C^3CH_2CH_3$ at δ 0 81 (t, J = 7 4 Hz) and a small positive effect for $C^3CH_2CH_3$ at δ 2 45-2 22 This indicates a cis relationship between C^{12b} and the ethyl-function at C^3 (in the major diastereomer) MS Found 340 1441 Calc for $C_{19}H_{20}N_2O_4$ 340 1424

Methyl-2-(phenylthio)butyrate (17) [19,20]
Sodium (1 38 g, 60 mmol) was dissolved in 100 ml dry MeOH (-5 °C under nitrogen) To the solution was added 60 mmol thiophenol, which was distilled before use After 15 min, 60 mmol of methyl 2-bromobutyrate [15] (10 86 g) was added to the reaction mixture After stirring for 2 hr at 20 °C, the solvent was evaporated and the residue was filtered through a short SiO_2 column with EtOAc as the eluent Evaporation of the solvent and a bulb to bulb distillation (100°C/) 1 mm) gave a colourless oil 17 Yield 12 0 g (95%) IR($CHCl_3$) 1729 (s), 1582 (w), 1458 (s), 1436 (s), 1160 (s), 688 (s) PMR($CDCl_3$, 60 MHz) 0 98 (t, J = 7 5 Hz, 3H, C^4H), 2 16-1 60 (m, 2H, C^3H), 3 47 (t, J = 7 5 Hz, 1H, C^2H), 3 62 (s, 3H, $COOCH_3$), 7 66-7 15 (m, 5H, s-ArH) FD = 210 (M^+) $C_{11}H_{14}O_2S$

3-Ethyl-4-hydroxy-1-[2-(3-indolyl-1-phenylthio)ethyl]-2-pyridone (18)
To a stirred solution of 0 59 mmol NaH in 15 ml THF was added 250 mg (0 59 mmol) of 7c dissolved in 2 ml THF (T = -40 °C, under nitrogen) No reaction was objected at -40 °C for 2 hr (TLC EtOAc/CH_2Cl_2 on SiO_2) At -15 °C (0 5 hr) two products were formed, compound 18 and the more polar compound 14 After an additional stirring for 2 5 hr at 0 °C a concentrated NH_4Cl/H_2O soln was added to the mixture Et_2O extraction followed by NaCl treatment, drying over Na_2SO_4 and evaporation of the solvent gave the crude products Chromatography on SiO_2 with EtOAc/CH_2Cl_2 (1 2 → 1 1) gave two crystalline products which were both recrystallized from EtOAc 18 Yield 90 mg (39%), mp 180-181 °C (from EtOAc) 14 Yield 68 mg (40 8%), mp 189-191 °C (from EtOAc) 18 IR($CHCl_3$) 3600 (w), 3500-3000 (w), 1645 and 1655 (s), 1622 (w), 1562-1550 (s), 1468 (s), 1442 (s), 1280 (s) PMR(CD_3CN + DMSO-d_6, 250 MHz) 0 95 (t, J = 7 4 Hz, 3H, $C^3CH_2CH_3$), 2 37-2 49 (m, 2H,$C^3CH_2CH_3$),3 05-3 10 (m, 2H, CH_2CH_2N), 4 04-4 10 (m, 2H, CH_2CH_2N), 5 71 (d, J = 7 5 Hz, 1H, C^3H), 6 88 (d, J = 7 5 Hz, 1H, C^5H), 6 87-6 91 (m, 2H, -SArC^{2}H, SArC^{6}H), 7 06 (s, 1H indole C^2H), 7 07-7 27 (m, 5H, indole C^5H, indole C^6H, -SArC^{3}H SArC H, sArC^{4}H), 7 47 (d, J = 7 8 Hz, 1H, indole C^7H), 7 60 (d, J= 7 5 Hz, 1H, indole C^4H), 11 0-8 0 (bs, 1H, C^3OH) The results of dr (double resonance) techniques were as follows irradiation of the multiplet of CH_2CH_2N at δ 3 05-3 10 gave a positive enhancement for the indole C^2H at δ 7 06 (relative to the aromatic protons), which is a result of loss of allylic coupling with CH_2CH_2N PMR(DMSO-d_6, 250 MHz) 0 97 (t, J = 7 4 Hz, 3H, $C^3CH_2CH_3$), 2 35-2 51 (m, 2H, $C^3CH_2CH_3$), 3 04-3 09 (m, 2H, CH_2CH_2N), 4 06-4 15 (m, 2H, CH_2CH_2N), 5 82 (d, J = 7 2 Hz, 1H,

C^5H), 6 97 (d, J = 7 2 Hz, 1H, C^6H), 6 99 (bs, 1H, indole C^2H), 7 14-7 36 (m, 7H, indole C^5H, indole C^6H, all aromatic protons of S-Ar), 7 51 (d, J = 8 1 Hz, 1H indole C^7H), 7 71 (d, J = 7 6 Hz, 1H, indole C^4H), 10 02 (s, 1H, C^4OH) MS Found 390 1385 Calc for $C_{23}H_{22}N_2O_2S_1$ 390 1402 Treatment of compound 18 with 10 eq $NaOCH_3$/THF at 20 °C gave an almost quantitative yield of 14 after 72 hr

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