STEREO- AND ENANTIOSELECTIVE SYNTHESES OF 2,3-DIHYDROINDOLE DERIVATIVES*

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Abstract — 2,3-Dihydroindoles (2,3-Indolines) can be obtained in a highly stereoselective fashion through 1,5-electrocyclization of ortho-substituted aminobenzenes. The scope and mechanism of this novel process are discussed and also some applications. In presence of chiral alcohols the ring closure proceeds with remarkably high enantioselectivity.

CONTENTS:

1. Introduction

The importance of a key structural element in natural product chemistry is often reflected by multiple syntheses for it. Despite the already impressive number of well-established indole syntheses[1] the recent years have witnessed a steady growth in novel procedures[2] most of which lead to structurally varied derivatives of the aromatic parent compound. In contrast herewith 2,3-dihydroindole (2,3-indoline) although often present in natural products[3] has received

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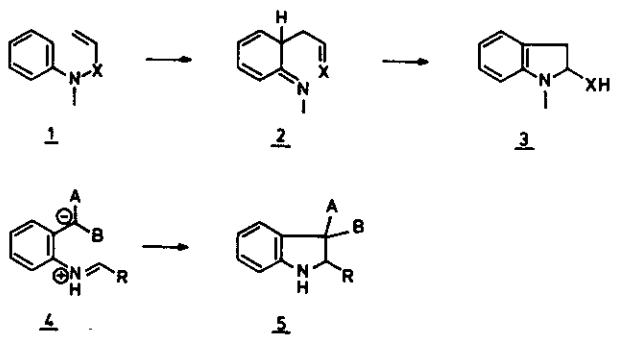
much less attention presumably because of the more facile synthesis of indoles by subsequent eliminative aromatization. Most indole syntheses are based on the sigmatropic rearrangement $\underset{\sim}{1} \rightarrow \underset{\sim}{2}$, followed by intramolecular addition $\underset{\sim}{2} \rightarrow \underset{\sim}{3}$. Thus in this type of reaction the C_3-C_{3a} bond is made up first while ring closure occurs by subsequent N-C bond formation.

An entirely different process is represented by the cylization $\underset{\sim}{4} \rightarrow \underset{\sim}{5}$ in which the C_2-C_3 bond is directly set up by nucleophilic addition to the imine in a formal 5-<u>endo</u>-trig[4] type of ring closure. However, since the carbon atoms to be joined are part of a conjugated π-system of 5 atoms with 6π electrons the addition reaction can also be classified as a 1,5-electrocyclization. In the sequel it will be shown that the latter representation most probably is the correct one. The general theory on 1,5-electrocyclic reactions has been recently reviewed[5] and will not be dealt with here. Only one important conclusion may be emphasized again which refers to the stereochemistry of the process. In view of its electronic nature as a 6π type electrocyclic reaction the bond formation should occur in a disrotatory mode[6] which bears definite stereochemical consequences for the product. Such a rule is of great value for practical applications of the novel method for indoline formation.



1 2 3

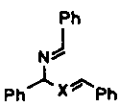
4 5

2. *Imine 1,5-Electrocyclic Reactions*

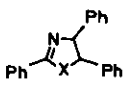
One of the oldest examples of the electrocyclic bond formation of imines was described in 1844 by Laurent[7]. The diimine $\underset{\sim}{6}$ cyclized in the presence of tert-BuOK/tert-BuOH at 30°C to <u>cis</u>-imidazoline $\underset{\sim}{7}$ which at higher temperature

isomerized to the trans isomer 8. Use of a stronger base, e.g. LDA in THF at -120°C, enhanced the rate of cyclization of the anion of 6 producing exclusively the cis isomer 7[8].

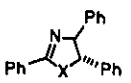
Surprisingly the low energy (E) → (Z) isomerization of the imine 6 is not reflected to any extent in the product formation. A different situation is encountered in the cyclization of 9. The slower bond formation allows E - Z isomerization of the imine to compete and consequently a mixture of imidazoles 10 and 11 is obtained. This important result proves beyond any doubt that both (E)- and (Z)-imines may cyclize.



6 X = N
9 X = CH



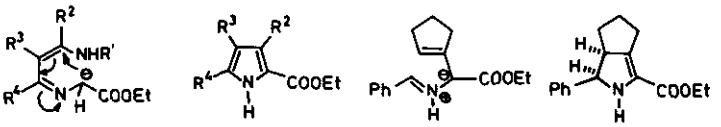
7 X = NH
10 X = CH_2



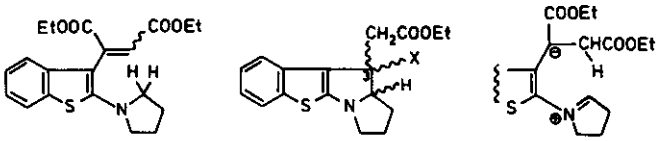
8 X = NH
11 X = CH_2

Other imine 1,5-electrocyclizations include the synthesis of 1-H-pyrrole-2-carboxylates 13 via azabutadienes 12[9] and the formation of dihydropyrroles 15 by ring closure of the 1,3-dipolar intermediate 14 which in turn is generated from the Schiff base of an amino acid ester and benzaldehyde[10]. The stereochemistry of 15 again pointed to a disrotatory cyclization of the more stable E-iminium isomer 14. A most interesting example is found in the behaviour of pyrrolidine 16 which upon heating in toluene exclusively gives a single stereoisomer 17[11]. Reflux in a more polar solvent (butan-1-ol) of 16 affords a 1:2 mixture of 17 and 18. Similar findings have been obtained in studies on related compounds. As has been proven from experiments with deuterated pyrrolidines a stereospecific hydride transfer[12] takes place leading to the 1,5-dipole 19. Depending on the type of solvent which influences the lifetime of the intermediate the disrotatory cyclization then occurs from either carbanion conformation leading to the products 17 and/or 18.

In the next section we describe our own work in the field of imine 1,5-electrocyclization and the application of this reaction to the synthesis of alkaloids



12 13 14 15



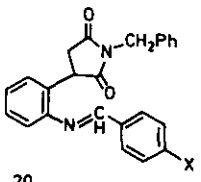
16 17 X = C_3-β COOEt 18 X = C_3-α COOEt 19

and mitomycine analogues. In view of the strong resemblance of the 1,5-electrocyclization to the extensively documented 1,3-dipolar cycloaddition[13] many results are expected to follow.

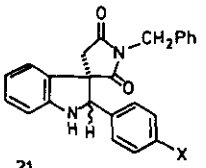
3. Indoline Synthesis. Practical Applications

Upon refluxing 20a in xylene a high yield cyclization occurs to the pure indoline isomer 21a. We assume that the dipolar system 23 acts as an intermediate in a 1,5-electrocyclization reaction. Surprisingly imine 20b does not cyclize under the same conditions. The important difference between 20a and 20b may be the base strength of the imine nitrogen. Probably imine 20b is not basic enough to transform into the required dipolar intermediate 23. This result shows that subtle electronic effects exert great influence on the outcome of the cyclization experiments. One of the possible ways for facilitating the proton transfer to the imine nitrogen may be considered the raise in acid strength of the

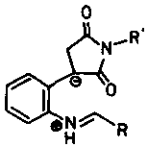
proton. This can be easily accomplished by taking different electron-withdrawing groups for X and Y. Thus cyclization of 24 to the indoline 25 occurs spontaneously upon preparing the imine. An indirect proof for the importance of a sufficient acid strength also follows from the observation that compounds of type 26 and 27 cannot be cyclized under a variety of (basic)



20 a X = OMe
b X = H



21 a α-H X = OMe
b β-H X = OMe
c α-H X = H
d β-H X = H



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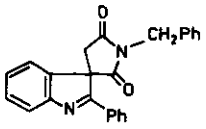
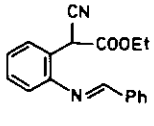


22

conditions. Alternatively the proton transfer can be assisted by adding a weak external base as for instance a tertiary amine. Indeed it is found that cyclization of 20b takes place quantitatively in refluxing toluene in the presence of a catalytic amount of triethylamine. Again a single stereoisomer 21c is formed. Lastly the catalysis may also occur by Lewis acids[14] as is shown by the result of the reaction of 20b with $Zn(OAc)_2$ in refluxing toluene. Most interestingly in the latter experiment also a considerable amount (cis/trans 4:1) of the spirocyclic trans isomer 21d is formed.

In connection with the latter reaction it is worth noting that reflux of indolines of type 21 in an acid medium in the presence of oxygen leads to indolenine 22, a result which can be substantiated (70% yield) when 21a is heated in toluene at 80°C for 1 hr in the presence of 3 equiv. of trifluoroacetic acid. Hydrogenation of 22 (Pd/C) gave an 85:15 mixture of 21c and 21d. In view of the facile addition to indolenines[15] the oxidation reaction may have some practical significance.



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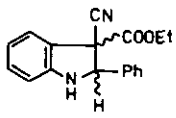

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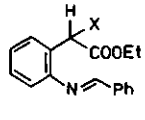
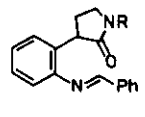
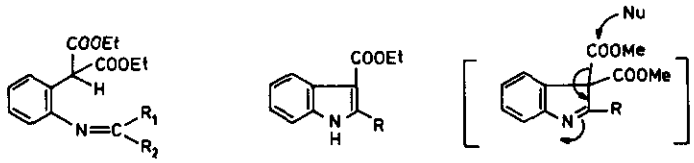


26 X = H, CH_3



27 R = H, CH_2Ph

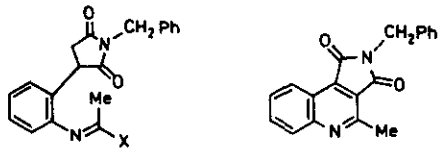
The cyclization of iminoesters 28a and 31 has been studied in connection with the known behaviour[16] of aromatic iminoesters in the presence of strong bases. As homologs of the aldimines discussed above it seems of interest to compare the reactivities of both type of imines. The iminoester 28a, prepared from the reaction of the corresponding amine and 1,1-dimethoxyethene, undergoes cyclization to indole ester 29a, in 60% yield presumably via 1,5-electrocyclization followed by dealkoxycarbonylation[17] of the intermediate indolenine 30a, upon treatment with *LiOtertBu in tertBuOH* at 82°C.



28 a $R_1 = OCH_3$, $R_2 = CH_3$
b $R_1 = H$, $R_2 = C(Cl)(CH_3)_2$

29 a R = CH_3
b R = $C(Cl)(CH_3)_2$

30 a R = CH_3
b R = $C(CH_3)_2$ (Cl)



31 a X = OMe
31 b X = SEt

32

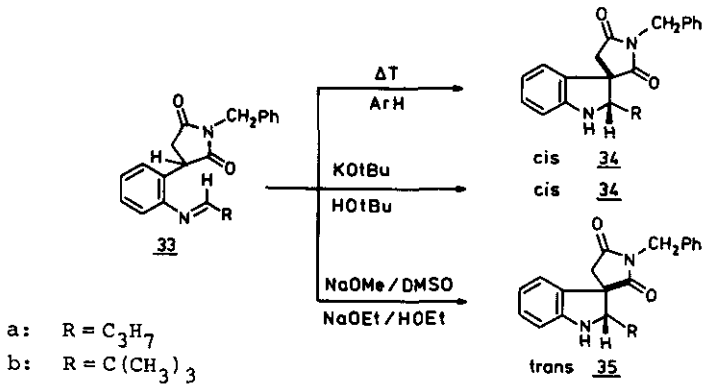
An analogous process is observed in the cyclization of imine 28b which affords the indole 29b in 42% yield. Most likely 29b is formed by a dealkoxycarbonylation of 30b which in turn may arise from the initially formed indoline by oxidation. On the contrary, the corresponding iminoester 31a solely affords (65% yield) the quinoline 32 upon treatment with LiOtertBu in tertBuOH/DMSO at 20°C. Most likely the difference in acidity of both types of imide hydrogens is insufficient to preferentially form the tertiary carbanion. A fast 6-endo-Trig cyclization followed by rapid air oxidation of the dihydroquinoline formed then accounts for the product. Similar results are obtained by starting from the iminothioester[18] 31b which also gives 32 in 86% yield. As a conclusion it may be stated that although intramolecular cyclizations of iminoesters appear to be possible, the facile RXH elimination followed by aromatization prevents isolation of the 2,3-indolines. The latter

cyclizations have been carried out in a strongly base medium. Since in terms of the mechanism no differences exist between the 1,5-electrocyclization of a 1,5-dipole or a pentadienyl type anion[19] the stereochemical results of both types of reactions are fully comparable.

The use of strong bases in the cyclization of aldimines leads to indolines in a highly stereoselective process which depends on the type of (alcohol)solvent used. Thus for the stereochemistry of indoline formation the following general scheme can be given (Fig. 1).

FIGURE 1

STEREOCHEMISTRY OF INDOLENIN SYNTHESIS



The origin of the stereoselectivity will be extensively discussed in the sequel (section 4). Important practical implications are the following. Aromatic and aliphatic aldehydes completely follow the rules and some representative examples are summarized in Table I. Of added synthetic potential is the cyclization of imines derived from aldehydes possessing functional groups. Thus the indoline 36 has been prepared by LiOtertBu catalyzed cyclization of the corresponding imine[20]. Upon subsequent treatment with acid at 0°C a quantitative cyclization to the novel type of pyrrolo[1,2-c]indole 37 occurs. Similarly, indoline 38 is obtained[21] in 85% yield as a 1:1 mixture of C_α-epimers. In connection with the latter result the reaction has also been investigated with 2-benzyloxy-2-phenylacetaldehyde[32]. The electrocyclization of the imine derived from the latter aldehyde proceeds

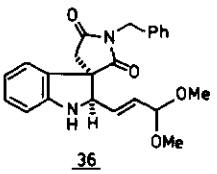
TABLE I

BASE-CATALYZED 1,5-ELECTROCYCLIZATION OF IMINES 33

R	Conditions	Yield %	Type Indoline	m.p. °C
C_6H_5	HOEt/NaOEt r.t.	90	35	158-160
C_6H_5	HO-t-Bu/NaO-t-Bu r.t.	71	34	217-219
	HOEt/NaOEt r.t.	89	35	oil
	HO-t-Bu/NaO-t-Bu THF 0°C	49	34	184-186
(E)-CH = CHPh	DMSO/MeONa	47	35	155-156
(E)-CH = CHPh	HO-t-Bu/NaO-t-Bu	80	34	216-219
$-CH_2CH_2C \equiv CCH_2CH_2OCH_2Ph$	DMSO/MeONa	73	35	82-83
$-CH_2CH_2C \equiv CCH_2CH_2OCH_2Ph$	HO-t-Bu/NaO-t-Bu	55	34	oil

with excellent stereoselectivity at low temperature. At -10°C (10 min) in presence of LiOtertBu/HOtertBu/THF cyclization takes place to the cis isomer 39 which is obtained in 82% yield as a mixture of C_α-epimers. Lowering of the temperature, however, results in a dramatic improvement of the diastereomer ratio. At -78°C (16 hr) followed by additional stirring at -40°C (1 hr) a yield of 90% of the cis isomer 39 is obtained in which the diastereomer ratio is 9:1. To secure the stereochemistry assigned trans isomer 40 has been prepared in 81% yield as a 1:1 mixture of diastereomers by cyclization in HOEt/LiOEt at 5°C for 64 hr. Thus, additional control proves to be possible on the stereochemistry of centres adjacent to the newly formed C-C bond. Moreover, the presence of α-oxy substituents is of some importance in regard with possible applications in the synthesis of Aspidosperma alkaloids.

Also base-sensitive aldehydes can be used in electrocyclization of the type discussed. A noteworthy example is the benzoate of glutacon aldehyde[23] the imine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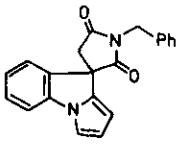
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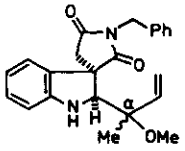
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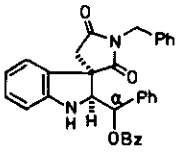
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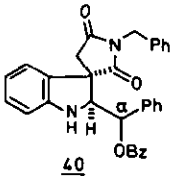
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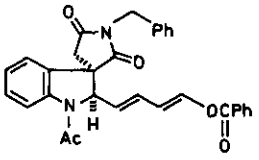
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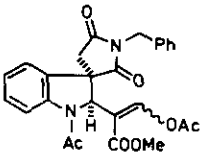
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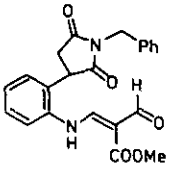
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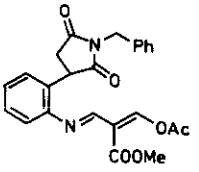
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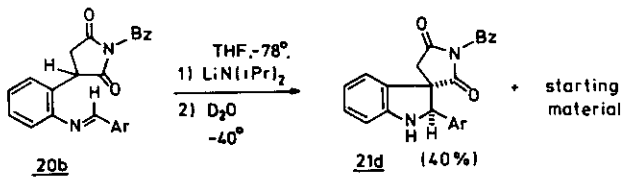
of which undergoes ring closure to indoline 41 upon reflux in toluene in the presence of triethylamine and acylation (CH_3COCl) of the indoline nitrogen. A similar sequence is followed in the preparation of 42[24] although cyclization takes place upon warming to 70°C. With ^{15}N-NMR it has been shown that the intermediate is the enamino-aldehyde 43. Although a cyclization of 43 now formally can take place via a 5-exo-Trig Michael addition, treatment of 43 under a variety of basic conditions does not afford a trace of indoline and only decomposition is observed. On the contrary, reaction in the presence of acetic anhydride/triethylamine produces a good yield of 42 as an E/Z mixture of enol acetates. Presumably the enamino-aldehyde is converted back to imine 44 which cyclizes in a 1,5-electrocyclization. The latter result reinforces the concept of an electrocyclic reaction as the mechanistic rationale and disfavors a simple 5-endo-Trig carbanion addition.

4. Indoline Synthesis. Mechanistic Aspects and Stereochemistry

In order to rationalize the results obtained so far, in particular the notable solvent effect in the base-catalyzed variant of the 1,5-electrocyclization, some additional studies have been performed. Firstly an experiment in which 20b is treated at -70°C with 1 equiv. of LDA in THF and subsequently quenched with D_2O at -40°C shows no incorporation of deuterium in the starting material while in addition 40% of the trans indoline 21d is formed (Fig. 2).

FIGURE 2

D_2O QUENCHING 1,5-ELECTROCYCLIZATION



20b 21d (40%)

TABLE II

CYCLIZATION OF 33 TO 34 AND 35 R = $C(CH_3)_3$ in THF

Entry	Base[a]	tertBuOH	Yield[b]	Ratio 34:35[b]
1	1 eq. LDA	-	20%	1:25
2	1 eq. LDA	1.5 equiv.	30%	1:1
3	1 eq. LDA	3 equiv.	30%	2:1
4	1. eq. LiOtertBu[c]	3 equiv.	80%	7:1

[a] Reaction conditions: addition LDA and tert.butanol at -78°C, mixture allowed to warm to 0°C (3 hr) and to 20°C (1 hr)

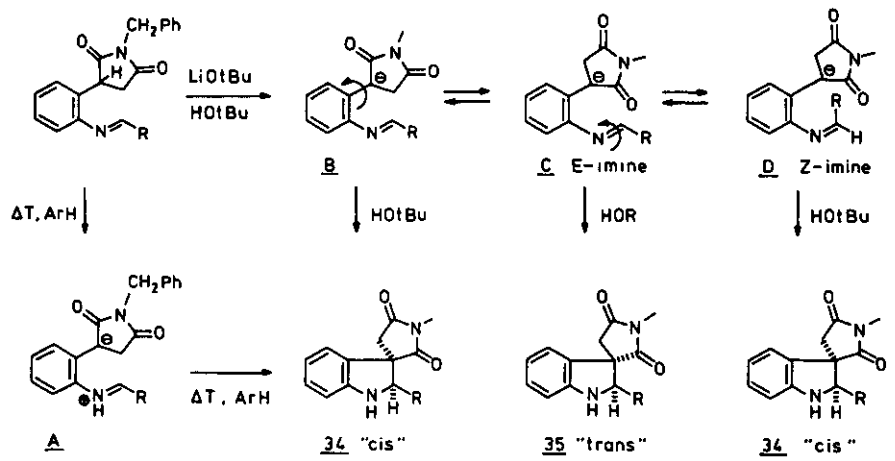
[b] Determined by 'H NMR

[c] Solvent tertBuOH-THF. Addition 1 equiv. of BuLi at -70°C. Mixture allowed to warm to 0°C (3 hr) and subsequently to 20°C (1 hr).

Thus once the carbanion has been formed it immediately cyclizes to the indoline. Secondly in a series of parallel experiments, the LDA-THF-imine system is generated at -70°C after which the temperature is raised in 10 min to 0°C, subsequently kept for 3 hr at 0°C and additionally 1 hr at 20°C. As shown in Table II the main product formed in 20% yield proves to be the trans isomer 35 (Entry 1). Repetition of the experiment in the presence of various amounts of tert-butanol exhibits a significant increase in the percentage cis isomer 34 and a drop in 35 (Entries 2 and 3). Omission of LDA finally strongly raises the yield of 34 (Entry 4). At -78°C no cyclization occurs and the imine is recovered. Two additional comments can be made on these results: (i) in all experiments a proportion of the trans isomer 35 is formed and (ii) the diisopropylamine competes with the imine in complexing tert-butanol and thus the presence of an amine has an unfavourable effect on the stereoselectivity. From the data in the Tables I and II a decisive influence of the structure of the alcohol on the stereochemical course of the reaction is highly conspicuous and not easily reconciled with a mere solvent effect. Instead a more likely explanation encompasses the role of the alcohol as some sort of complexing agent (Vide infra). To account for the formation of indolines via the 1,5-electrocyclization process, the following scheme is proposed.

FIGURE 3

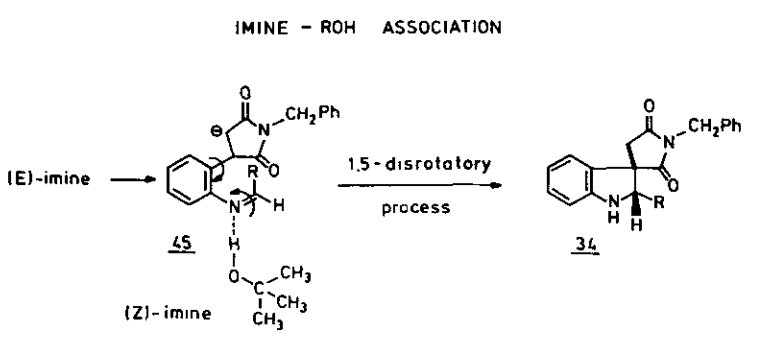
ORIGIN OF STEREOSELECTIVE 1,5-ELECTROCYCLIZATION



We assume that in the thermal reaction, proton transfer occurs most easily from the conformation of 33 as shown in Fig. 3, to afford the dipolar intermediate A with the enolate oxygen away from the E-imine function. Once A has been formed, it immediately cyclizes in a disrotatory fashion to yield the cis indoline 34. Most probably the lifetime of A is so short, that conformational changes in A do not occur. The situation is different in the case of enolate B. The lifetime of B is longer due to the low temperature at which it is generated and to the presence of a polar solvent stabilizing the intermediate. Therefore, B has time to equilibrate to C which on disrotatory cyclization affords the trans isomer 35. A possible reason for predominant electrocyclization from C (See Table) could be product development control, as trans isomer 35 is more stable than cis isomer 34.

One puzzling factor, however, remains to be solved which is the behaviour of the carbanion in tert-butanol. Since a priori the polarity of the latter solvent will be of the same order as for other alcoholic solvents, the exclusive formation of the cis isomer 34 seems difficult to explain. A closer analysis, however, suggests two possible modes of reaction. Either the enolate reacts in the conformation B or the imine geometry changes from (E) to (Z) forming an alternative "Inside Enolate" D before cyclization takes place. In the following conclusive evidence is presented to support the latter explanation. Imines are known to associate with alcohols by hydrogen bonding[25]. It is known that by way of such interaction sterically hindered hydroxyl groups like tert-butanol can alter the E,Z-isomer ratio resulting in a substantial increase of the amount of (Z)-isomer[26]. Such complexation can be visualized as in 45 and the stereochemical outcome of the disrotatory cyclization of the "Inside Enolate/(Z)-imine" will be the formation of the cis product 34 (Fig. 4).

FIGURE 4



In order to obtain more evidence for the important role of alcohol structure in the electrocyclization, the process was carried out in the presence of the optically active alcohols (-)-menthol and (-)-borneol. Modest enantioselectivity[27] was observed as shown in Table III. This undoubtedly signifies that there exists a tight complexation between alcohol and substrate in the TS of cyclization.

TABLE III

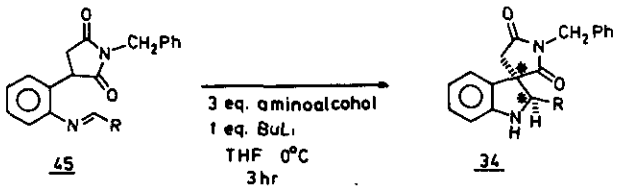
ASYMMETRIC SYNTHESIS OF 34

R	Alcohol	T °C	Time hr	Yield %	e.e. %
a: n-propyl	menthol	0°	1	40	17
b: t-butyl	menthol	0°	3	60	31
a: n-propyl	borneol	0°	1	70	17.5
b: t-butyl	borneol	0°	3	73	16.7

Since the complex 45 contains a Li-enolate structure in addition to the imine function a plausible extension of the complexing ability of the solvent may be found in the use of a bifunctional solvation catalyst[28] such as a β-hydroxyamine. In view of the known propensity of an amine to coordinate with $Li^{\oplus}$ cations, the use of a chiral alcohol also possessing an additional site for complexing the $Li^{\oplus}$ cation follows as an obvious next step. Upon use of (+)-N-Me-ephedrine the results surpassed our most sanguine expectation in the case of imine 45a. As follows from Table IV a quantitative yield of a single enantiomer (-)-34a is obtained upon cyclization of the corresponding imine 45a in the presence of 3 equiv. of (+)-N-methyl-ephedrine and 1 equiv. of n-BuLi in THF as a solvent. The introduction of different substituents on the amine nitrogen clearly reveals the dramatic influence of varying the steric parameters. In going from the N-ethyl- to the N-benzylephedrine a marked decrease in e.e. values is observed thereby suggesting the (partial) breakdown of the association complex as a result of steric interactions. In addition the modest e.e. values found upon cyclization of the tert-butylimine 45b leading

TABLE IV

BIFUNCTIONAL ASYMMETRIC CATALYSIS



	Alcohol	e.e. cis(-) %	Yield %
a: R = propyl	(+)-N-Me-ephedrine	100	65
	(+)-N-Et-ephedrine	68	64
	(+)-N-Benzylephedrine	26	48
	(+)-N-(2-Methoxyethyl)ephedrine	38	60
b: R = t-butyl	(+)-N-Me-ephedrine	37	70*
	(+)-N-Et-ephedrine	34	21*
	(+)-N-Bz-ephedrine	3	30*
	(+)-N-Mee-ephedrine	28	15*

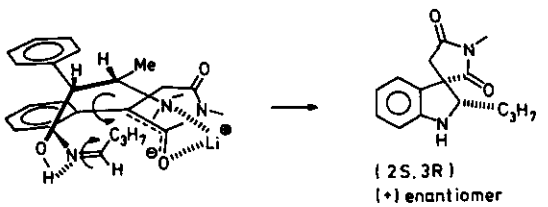
*trans isomer also formed

to indoline 34b once more emphasizes the sensitivity of the process towards steric factors[29]. From these results it is concluded that the "Inside Enolate" intermediate is highly plausible since for geometric reasons the formation of a two-dented complex with the alternative carbanion is impossible. From this it follows that in the 1,5-electrocyclization leading to the cis indoline 34 the (Z)-imine is involved. A structural consequence for the latter system is the necessary out of plane position of the imide and imine ortho substituents in view of severe steric interactions in the planar form. Therefore the "Inside Enolate" has to be

represented by a helix-type structure which is also required in the electrocyclization. As a final test for the correctness of this hypothesis it should be possible to construct models of the association complex which, in regard to the defined spatial structure of the catalyst, will predict the absolute configuration of the indoline (Fig. 5).

FIGURE 5

PREDICTED CONFIGURATION 1,5-ELECTROCYCLIZATION



(2S,3R)
(+) enantiomer

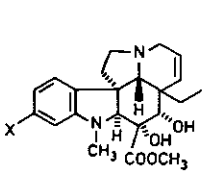
46 34

Since the latter is coupled with the known absolute stereochemistry of Aspidosperma alkaloids, a direct proof for the proposed sequence of events is available. Thus starting from (1R,2S)-(-)-N-methylephedrine and constructing the model 46 on the basis of O-H ··· N and $Li^{\oplus}$ ··· N interactions, the absolute configuration of the newly formed (+)-spiroindoline 34 will be (2S,3R). This is precisely what follows from a comparison of the Cotton effects of the reduced 34a (LAH reduction of both C=O functions gives the corresponding amine) and the natural aspidospermidines[30]. From the model it also follows that the subtle changes in the amine substitution pattern viz. replacement of methyl by other space demanding alkyl groups have unfavorable consequences for the stability of the complex. This result therefore strongly supports the postulated "Inside Enolate" intermediate. It also constitutes a unique example of solvent-induced enantio-selectivity in a carbon-carobon bond forming process.

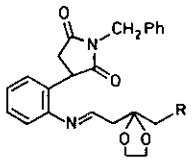
5. Applications

The method discussed before is a straightforward pathway to indole-type compounds. Given the high biological profile of various representatives of this

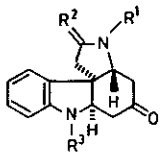
family, attempts have been focused on the synthesis of two important classes viz. the Aspidosperma alkaloids and the mitomycins. In the first class a formal total synthesis of vindorosine (47) and vindoline (48) has been accomplished[31] while in the second series a short route to a number of novel derivatives has been developed. Since the achievement in the alkaloid synthesis has been reviewed earlier, attention is focused on the efforts in the mitomycin series.



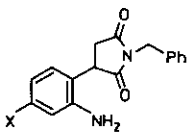
47 X = H
48 X = OH



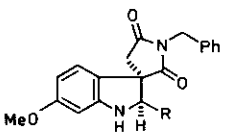
49 R = $COOC(CH_3)_3$
50 R = H



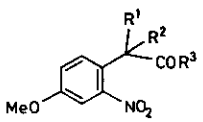
51 $R^1 = CH_2Ph$ $R^2 = O$ $R^3 = H$
52 $R^1 = COCH_3$ $R^2 = H_2$ $R^3 = CH_3$



53 X = H
54 X = OCH_3



55 R = C_6H_5
56 R = $CH_2C_6H_5$



57 $R^1 = CN$ $R^2 = H$ $R^3 = OC(CH_3)_3$
58 $R^1 = CN$ $R^2 = CH_2COOC_2H_5$ $R^3 = OC(CH_3)_3$
59 $R^1 = H$ $R^2 = CH_2COOC_2H_5$ $R^3 = NH_2$

5a Aspidosperma Alkaloids

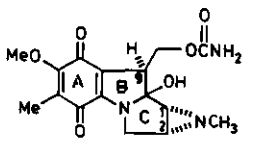
The synthesis of vindorosine proceeds from the tetracyclic lactam-ketone 51 which is obtained in three steps from the imine 49: (i) 0.5 equiv. BuLi, THF-tert-butanol, (ii) $NaBH_4/H^{\oplus}$, (iii) HCl-MeOH, ΔT. The imine in turn is prepared from the imide 53 and 3,3-ethylenedioxy-4-carbo-t-butoxy butanal[32]. The lactam 51 was transformed by standard operations into the known[33] intermediate 52 which has been already transformed into the alkaloid 47.

With regard to the possible enantioselective synthesis 51, it is of interest to mention the 1,5-electrocyclization of imine 50 under influence of BuLi/(-)-N-Me-ephedrine. The corresponding indoline is obtained in 60% yield and with a promising e.e. of 55%. This indoline can be converted into 51 by adaptation of the methodology outlined before so a formal asymmetric synthesis of vindorosine is also

at hand. In order to apply the synthetic scheme to the amine 54 a synthesis of the latter imide has to be developed. Since in the usual method an aromatic aldehyde is converted via the cyanoacetic acid ester route[34] and the necessary 2-NO_2-4-OMe benzaldehyde is difficult to obtain, an alternative pathway has to be developed. As a general and highly practical method, the malonate substitution of o-nitro-chlorobenzenes has been used, which via the nitro-aryl derivative 57 and additional reaction with ethyl chloroacetate leads to 58. Controlled hydrolysis (HBr-HCOOH) yields the amide 59 which upon treatment with base and catalytic hydrogenation gives imide 54. Since the latter amine upon imine formation and 1,5-electrocyclization affords compounds 55 and 56 in the manner described before, the effectiveness of the synthetic scheme towards the total synthesis of Aspidosperma alkaloids has been convincingly demonstrated.

5b Mytomicin Antibiotics and Analogues

The chemistry and pharmacology of the mitomycin antibiotics continues to receive wide-spread attention[35]. Since the strong antitumor and antibiotic activity of mitomycin B (60) is retained[36] in the corresponding easily-accessible mitosene 61, the efforts in total synthesis have mainly been concentrated on this type of compound. Extensive reviews on the chemistry of mitomycins have appeared[37]. Confirmatory evidence for the mechanism of the action of mitomycin C has recently been acquired[38] which points to a guanine cross-link formation at C-1. These data



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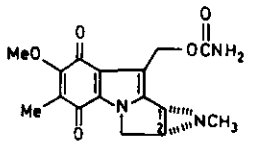
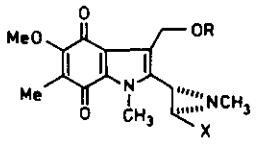
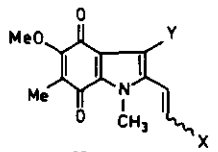


61

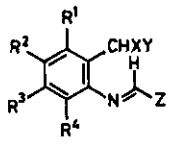


62



63

strongly call for the synthesis of novel variations of the mitosene structure 61. In addition with a view to the necessary bioreductive alkylation process for the activation of the mytomycin, the indoloquinones 62 and 63 are also considered as targets for total synthesis. Although a number of simple indoloquinones have been synthesized earlier as antibacterial agents using the Nenitzescu reaction[39], compounds of the types 62 and 63 have not been investigated with regard to potential cytostatic activity.



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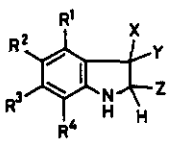

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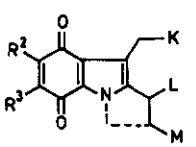

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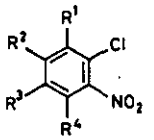
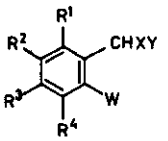




67 a $R^1 = R^2 = R^3 = R^4 = H$

b $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$

c $R^1 = R^4 = H$; $R^2 = OCH_3$, $R^3 = CH_3$

d $R^1 = R^4 = H$; $R^2 = R^3 = OCH_3$

e $R^1 = OCH_3$, $R^2 = R^4 = H$, $R^3 = CH_2OR$

68 $W = NO_2$; $X = CN$ $Y = COOC_2H_5$

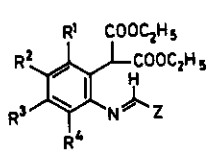
69 $W = NO_2$; $X = Y = COOC_2H_5$

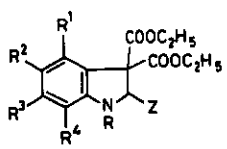
70 $W = NH_2$; $X = Y = COOC_2H_5$

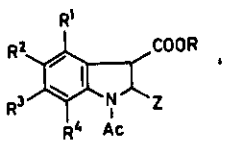
As described before the synthesis of pyrrolo[1,2-a]indoles like 37 is straightforward using the 1,5-electrocyclization process. In addition it has been mentioned that different types of indolines, e.g. 25, can be obtained by using the appropriate aldehyde precursor. Therefore a likely approach to the mitosenes consists of a 1,5-electrocyclization of imines of type 64 to the indolines 65 and subsequent transformation into indoloquinones and/or mitosenes 66. Such a strategy requires excellent availability of the starting indolines 65 and in this respect major achievements have been reached through the 1,5-electrocyclization technique. As a consequence of our approach the quinone functionality has to be introduced in the latter stages of synthesis.

As mentioned before, recent work in a second area of total synthesis mainly deals with the utility of the quinones as starting materials and several new routes to mitosenes based on the principle have been developed[40].

As the starting point the o-nitrochlorobenzenes 67a-e are selected in view of the anticipated facile conversion into the final quinone system and the potential for preparing modified ring A type mitosenes. The required diester 69 can be prepared directly from 67 by a nucleophilic aromatic substitution using malonate in HMPT/DMF[41]. Because of the low reactivity of the relatively electron-rich aromatic ring, high HMPT/DMF ratios and high temperatures have to be used. Therefore the alternative efficient two-step process 67 → 68 → 69 has been developed which generally affords the diesters 69 in combined yields of over 90%. The corresponding amines 70 are quantitatively obtained through careful hydrogenation at 3 atm in toluene/ethanol using PtO_2 as a catalyst. Under the latter conditions the undesired formation of the corresponding oxindole can be almost completely avoided.



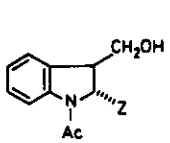




71 A : Z = $-C\equiv C-CH(OC_2H_5)_2$
B : Z = $-C\equiv C-CH_2OTHP$
C : Z = $-(E)-CH=CH-CH(OCH_3)_2$
D : Z = $-(E)-CH=CH-COOCH_3$
E : Z = $-(E)-CH=CH-C_6H_5$

72 R = H
73 R = $COCH_3$
74 R = $COOCH_3$

75 R = H
76 R = CH_3



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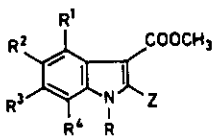
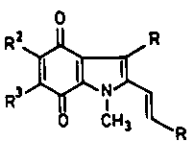


78 R = $COCH_3$
79 R = CH_3



80 R = $COOCH_3$
81 R = CH_2OH

a. $R^1 = R^2 = R^3 = R^4 = H$
b. $R^1 = R^3 = R^4 = H$ $R^2 = OCH_3$
c $R^1 = R^4 = H$ $R^2 = OCH_3$ $R^3 = CH_3$

As aldehydes ZCHO for the preparation of the imines 71A-71D those substituents Z are chosen which possess the required functionality for attaching the substituents L and/or M and/or forming the third ring. In model experiments reactions have also been carried out with cinnamaldehyde 71E.

Upon preparation of the imine 71E-b a spontaneous ring closure takes place which attests to the influence of the p-OCH_3 on the basicity of the imine-nitrogen. As pointed out before this basicity is one of the factors which determines the ease of the 1,5-electrocyclization. In all other cases 71A-71D a catalytic amount of base (NaOR) or Lewis acid ($Zn(OAc)_2$) in ethanol as a solvent suffices to complete the ring closure affording the indolines 72A-72D in nearly quantitative yields. The corresponding acetates 73 can be easily obtained upon reaction with Ac_2O; in order to prepare the carbamate 74, a two-step sequence is required consisting of an initial preparation of the N-COCl derivative ($COCl_2/N(C_2H_5)_3/PhCH_3$ followed by reaction with methanol/$N(C_2H_5)_3$. As a last general step mild hydrolysis (KOH/EtOH/H_2O/0°C) affords the indoline-3-carboxylic acids 75 in almost quantitative yield. The mitosane derivatives can now be prepared - as exemplified for 77 - by treatment of 75 with ethyl chloroformate in THF/$N(C_2H_5)_3$ solution and subsequent $NaBH_4$ reduction. The biologically more interesting mitosenes are also synthesized from the carboxylic acid 75. For instance esterification (Cs_2CO_3/$(CH_3)_2SO_4$/DMF) of 75D-b and oxidation with DDQ affords the indole 78D-b in excellent yield. In order to arrive at the quinone the N-Ac function is hydrolyzed and converted to the N-Me derivative 79D-b. The latter compound is transformed into the quinone 80b in the usual manner[42]: (i) HNO_3/HOAc, (ii) $Sn/HCl_{aq.}$/C_2H_5OH, (iii) Fremy's salt. At this point it can be stated that the overall yield of the process starting from 67b is 40% (13 steps). Finally the dihydroxy-compound is obtained by reduction of the quinone ($Na_2S_2O_4$/EtOH/H_2O) followed by DIBAH reduction in toluene and reoxidation of ring A to the quinone 81b. A similar scheme has been followed in the conversion of the corresponding methyl derivative 75D-c which leads to the quinone 81c.

CONCLUSION

The foregoing data amply demonstrate the synthetic possibilities of the 1,5-electrocyclic process as a general tool for the synthesis of a variety of indoline and indole derivatives. A unique stereoselectivity coupled with an experimentally

facile procedure and a flexible choice of the aldehyde precursor are important factors in the success of the method. Although the exact mechanism of this novel ring closure has to be proven in some additional details, the factors discussed strongly point to an electrocyclic process.

ACKNOWLEDGEMENT

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