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(19) (CA) **CANADIAN PATENT** (12)

(54) **A New Process for the Synthesis of 3', 4'-Anhydrovinblastine, Vinblastine and Vincristine**

(72) Kutney, James P., Canada
Choi, Lewis S. L., Canada
Nakano, Jun, Japan
Tsukamoto, Hiroki, Japan
Boulet, Camille A., Canada
McHugh, Michael, U.K.

(73) **UNIVERSITY OF BRITISH COLUMBIA, Canada**

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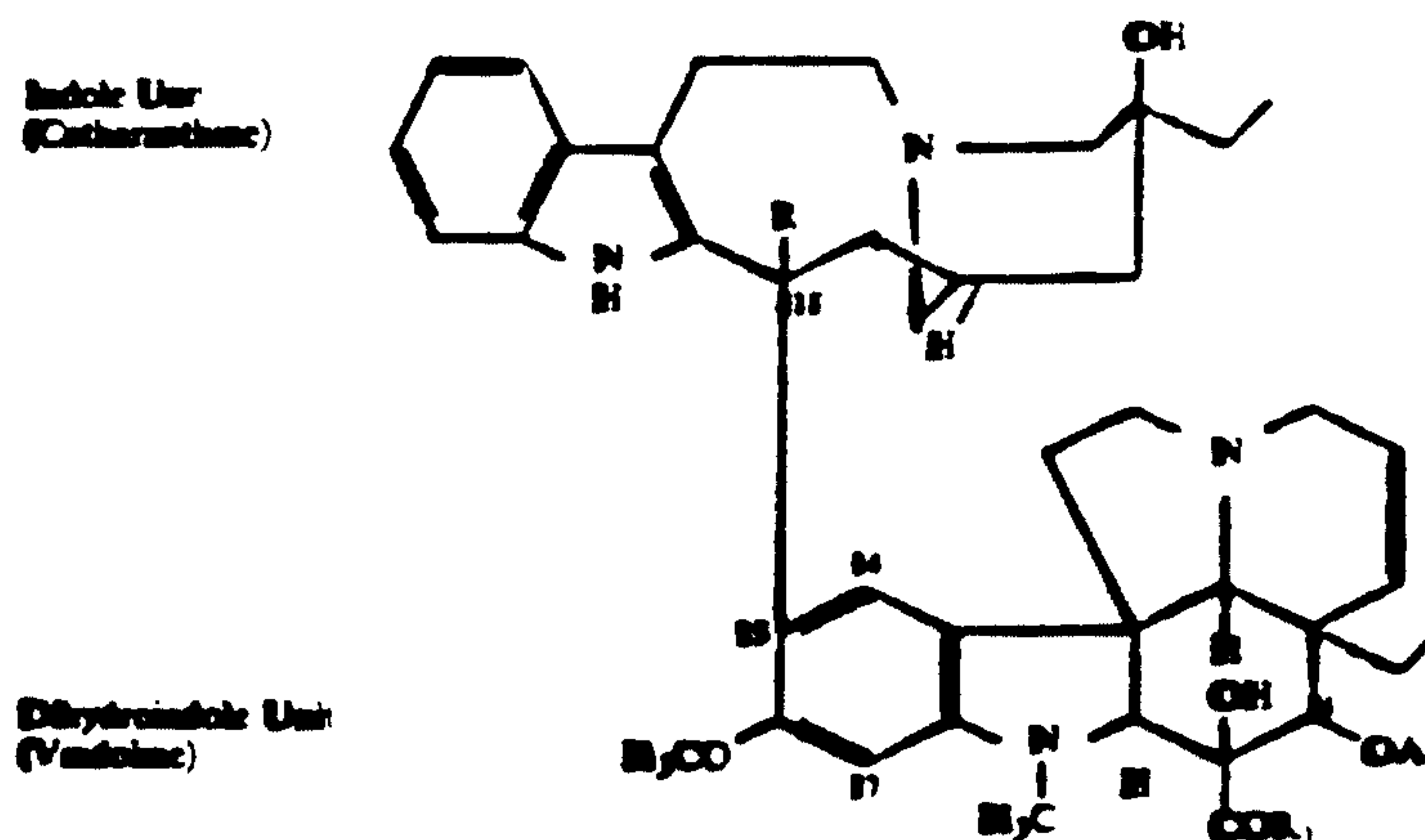
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ABSTRACT OF THE DISCLOSURE

The present application relates to a method for producing dimer alkaloid compounds especially of the Catharanthus (Vinca) alkaloid groups and, in particular, for producing the anti-viral, anti-leukemic (antineoplastic) compounds vincristine and vinblastine. Use of selected 1,4-dihydropyridine compounds for the 1,4-reduction of an iminium intermediate to an enamine results in significant increase in the yield of the enamine. Parameters for the oxidative transformation of enamine to the iminium intermediates and subsequent reduction of the iminium intermediates to vinblastine and leurosidine are disclosed. The overall process, conducted in a one-pot operation, producing vinblastine, leurosidine and 3',4'-dehydrovinblastine is described.

Process for the Synthesis of Vinblastine and VincristineField of the Invention

The present application relates to a further improvement of a new and improved method for producing dimer alkaloid compounds especially of the Catharanthus (Vinca) alkaloid groups and, in particular, is a further improved method for producing the anti-viral, anti-leukemic (antineoplastic) compounds, vincristine and vinblastine of Formula I.

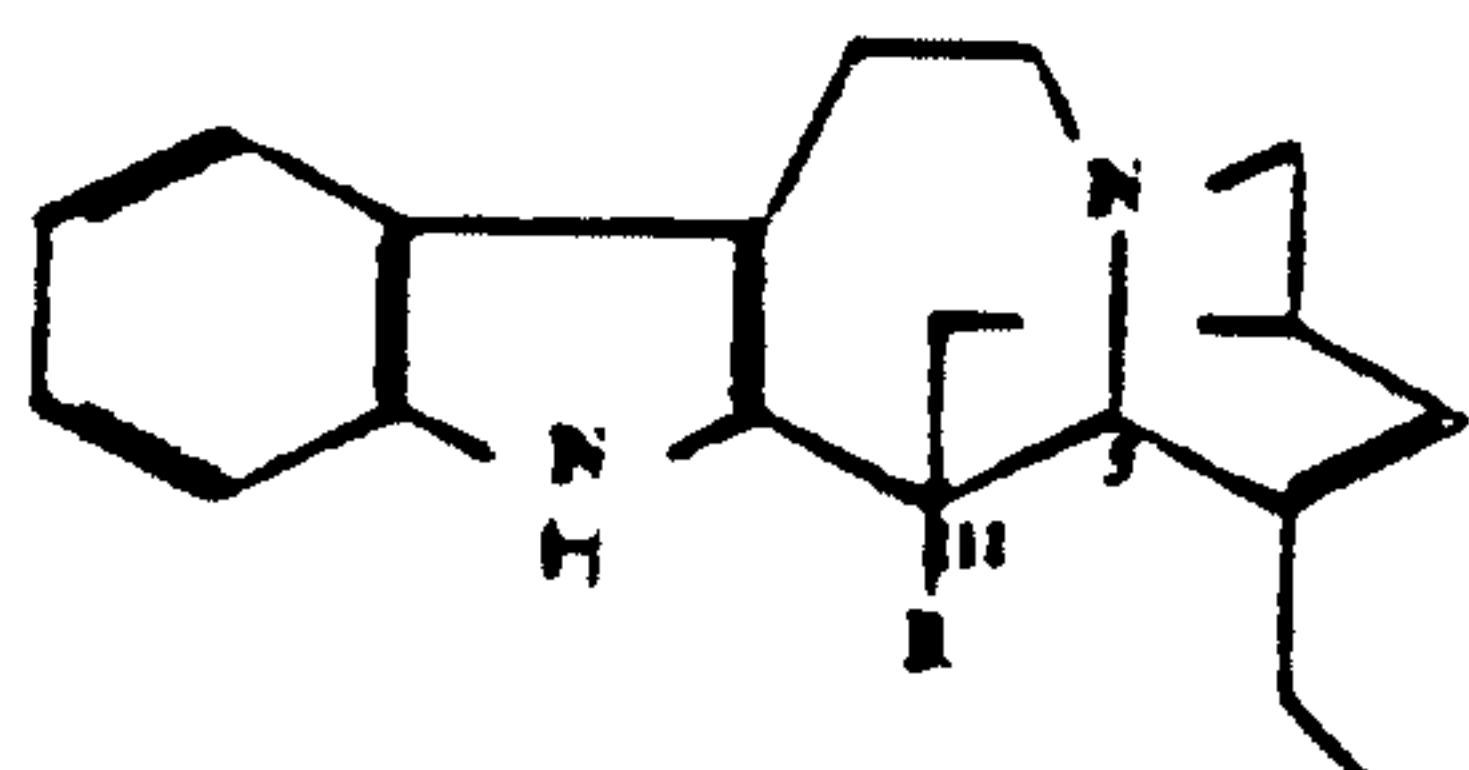


I

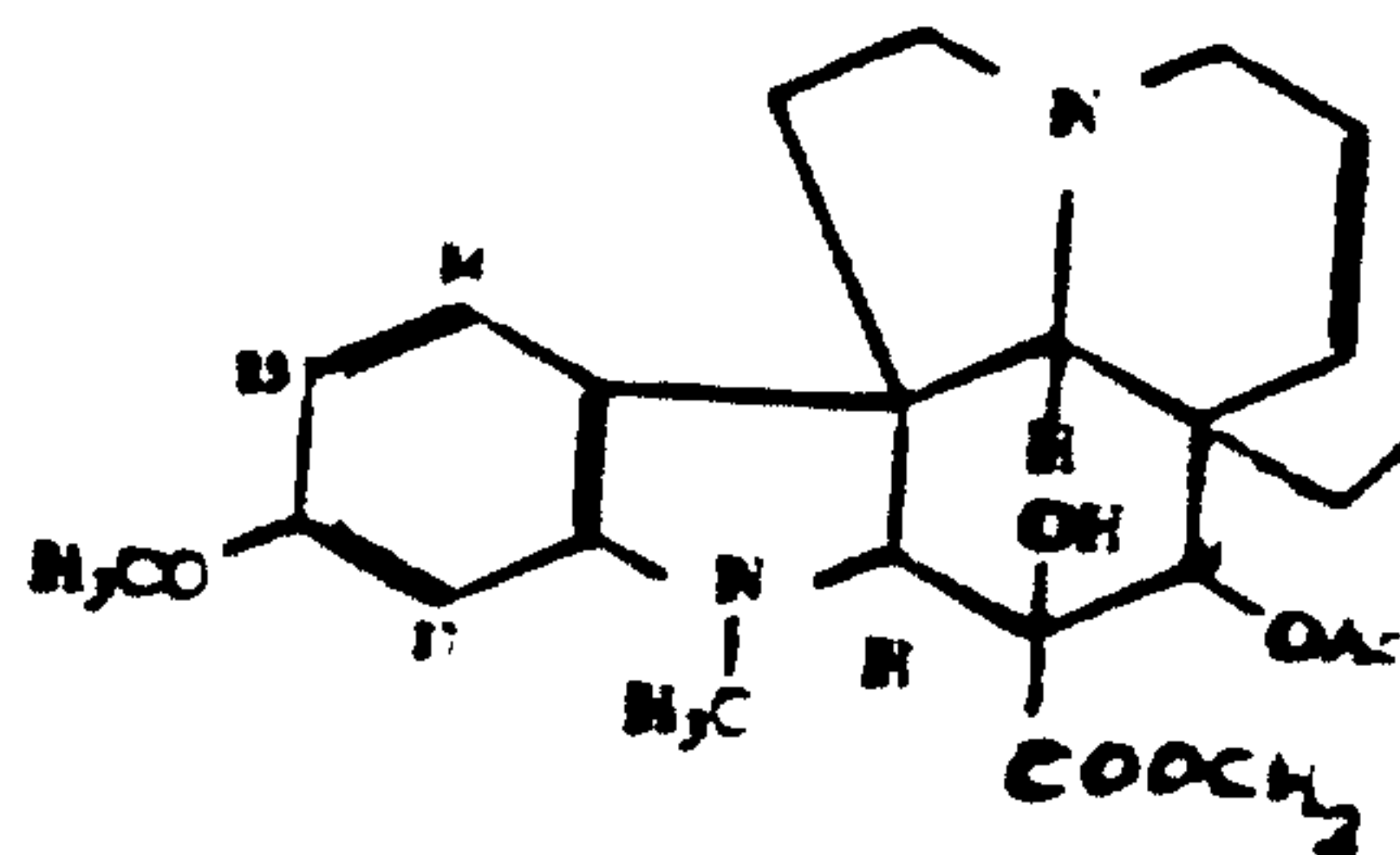
The above compound, when R is COOCH_3 , and R_1 is OCH_3 , is vinblastine (NSC 49482) and when R is COOCH_3 , and R_1 is OCH_3 and N_1 is N-CHO (N-formyl), vincristine (NSC 67574).

The present series of dimeric alkaloids, including important antitumor agents, are formed from an indole, such as catharanthine (Formula II, $\text{R} = \text{COOCH}_3$), and a dihydroindole unit, e.g., vindoline (Formula III), in which

the halves are linked via a carbon-carbon bond involving an aliphatic center C_{18} in the indole unit and an aromatic carbon C_{15} in the vindoline portion.



II

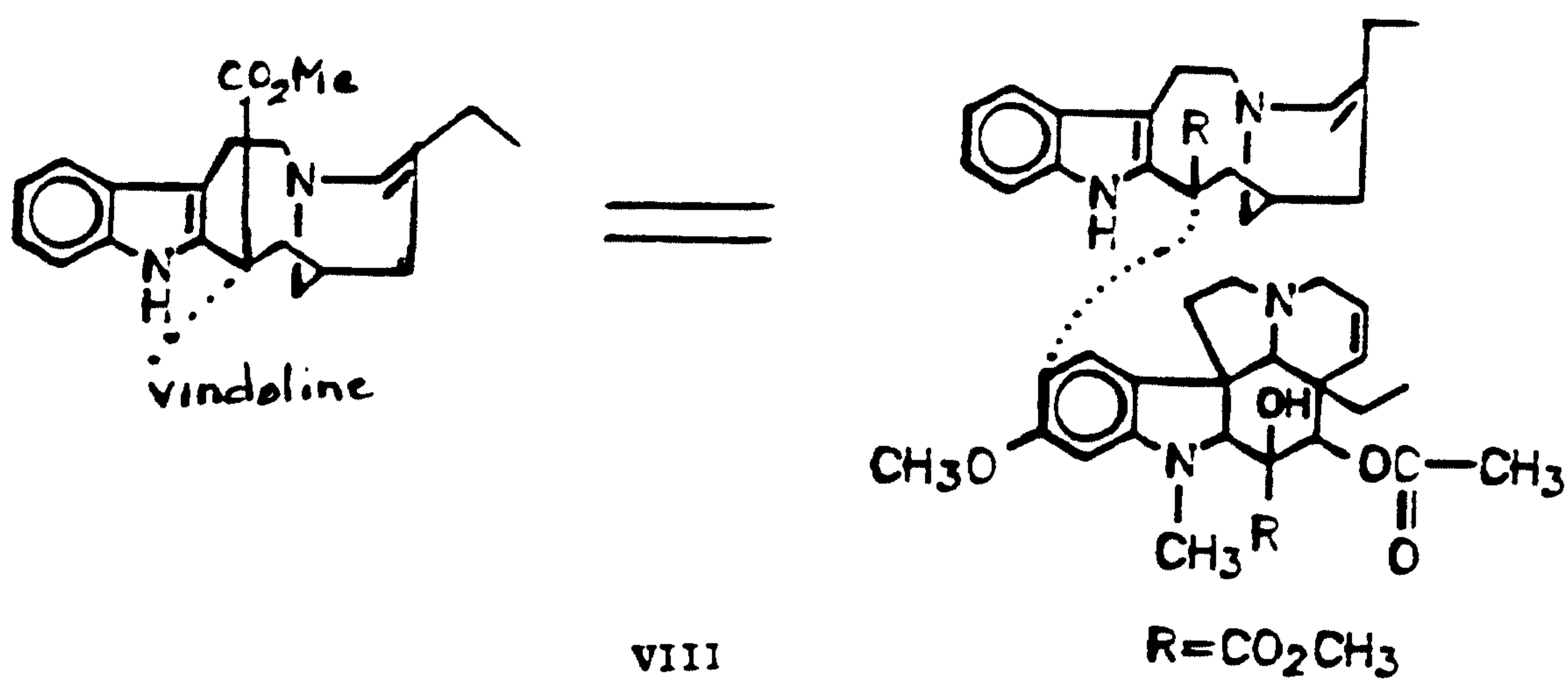
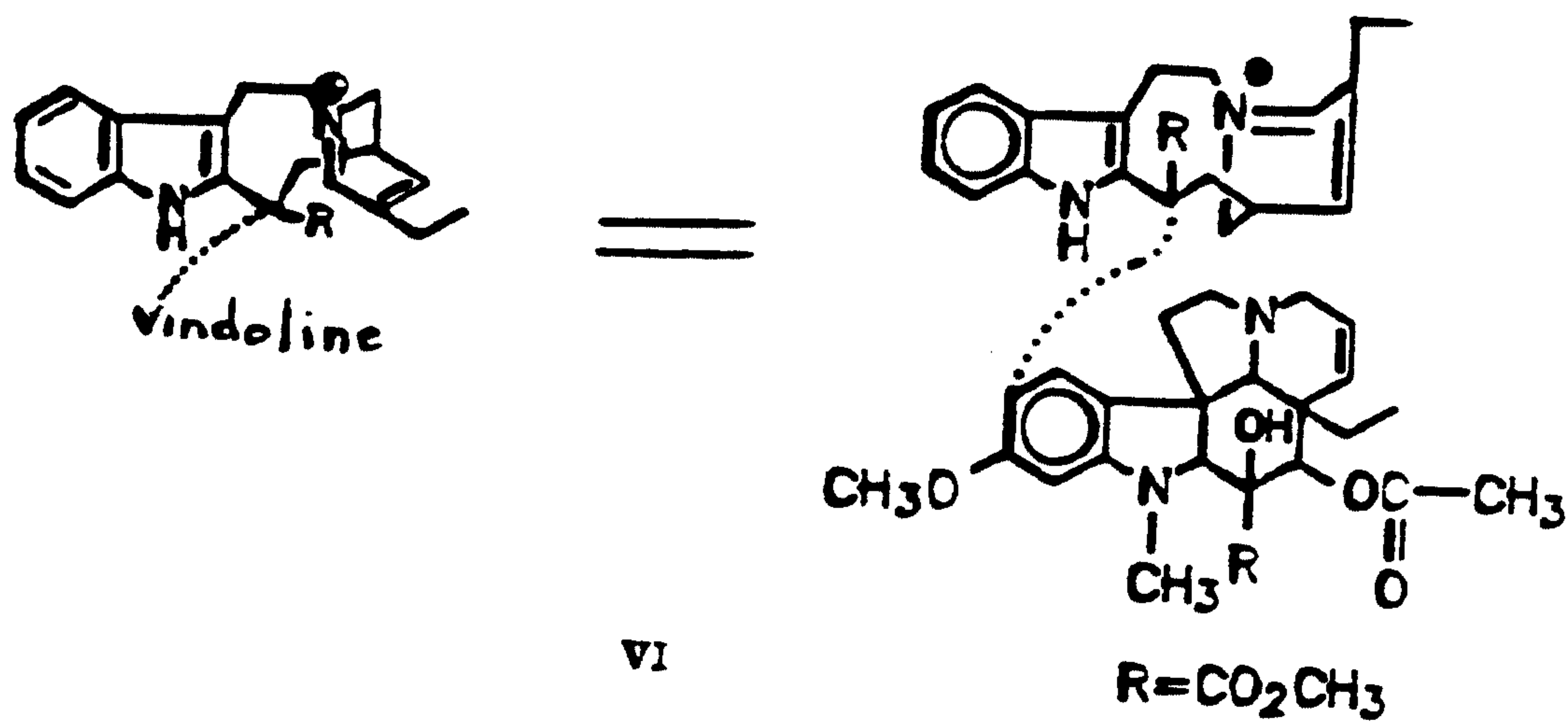


III

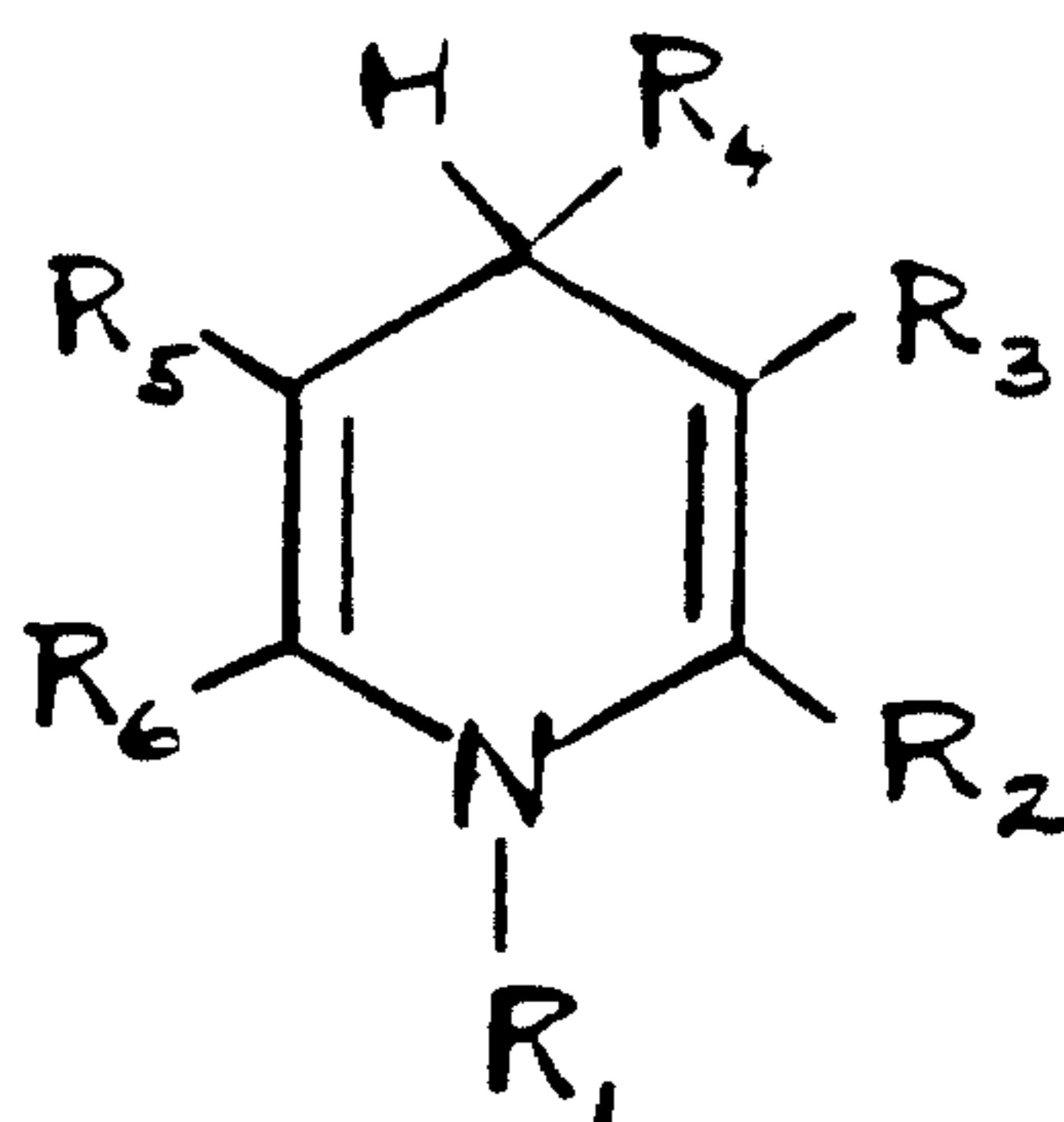
Summary of the Invention

The specific improvements in the present application are set out below.

Firstly, improvement of the novel reduction method, in which conversion of the iminium intermediate (Formula VI) to the enamine (Formula VIII)



as described in step (e), post, is achieved by the use of various new 1,4-dihydronicotinamides (Formula IX, $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$ and R_1 may contain different functional groups ;such as aryl, carboxylic esters, sugars, carboxylic acid, and carboxylate salt, as represented by Formulae XXVII to XXXII listed in Table 1) and 1,4-dihydropyridine compounds such as Formulae XXXIII and XXXIV. Of special importance is the presence of electron rich functional groups (e.g., carboxylic esters and carboxylate salts in R_1 of Formula IX, capable of coordination with the positively charged iminium intermediate (Formula VI). Such coordination increases both the regioselectivity (1,4-reduction over 1,2-reduction) and the rate of the reduction of iminium intermediate (Formula VI), leading to an improved yield of the enamine (Formula VIII). Further improvement in the formation of the latter compound is achieved by performing the reduction of iminium intermediate (Formula VI) and maintaining the reaction mixture before any subsequent manipulation at a low temperature (0 to -70°C) preferably below -40°C .



IX

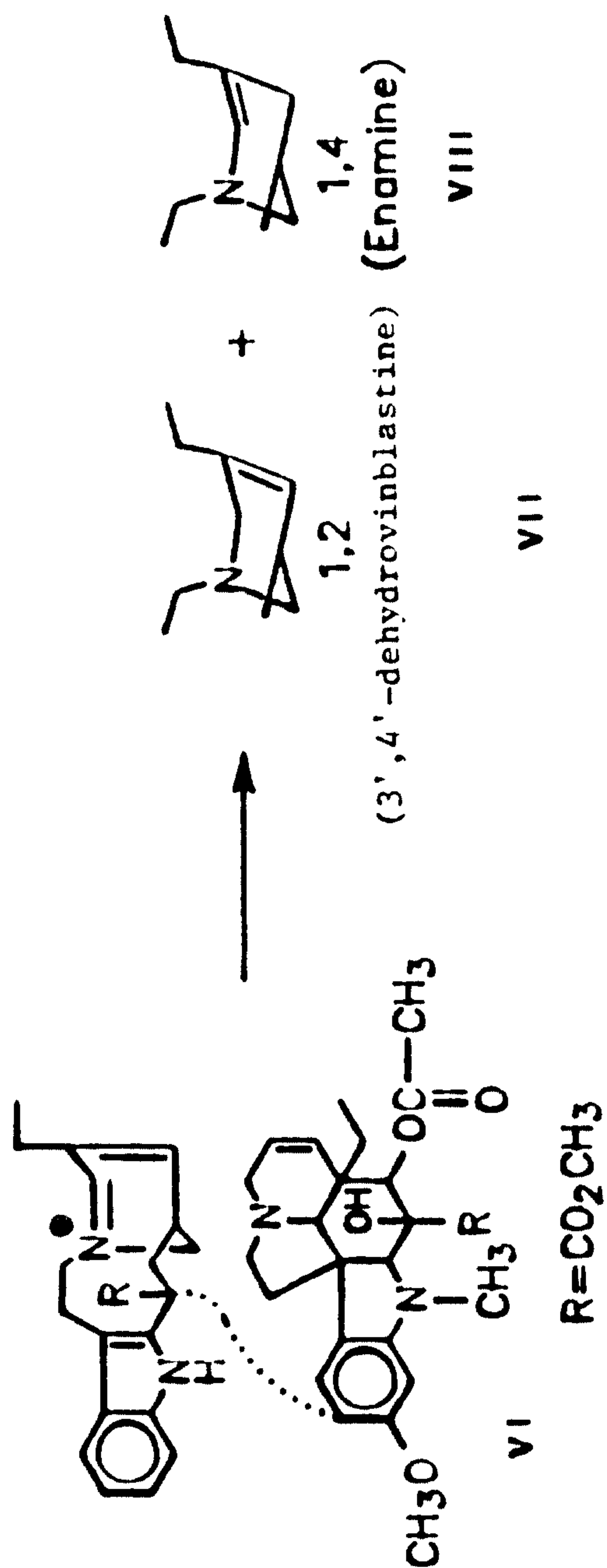
Specific examples related to the above improvements for the synthesis of enamine (Formula VIII) by the 1,4-reduction of the iminium intermediate (Formula VI) are given in the Examples 1-9 (Procedures C to K). Results of these examples are summarized in Tables 2 and 3. Table 2 indicates reduction procedures (Procedures I and J as in Examples 7 and 8), employing reducing agents Formula XXXI and Formula XXXII, respectively, afford the best yields of the enamine (Formula VIII). Table 3 shows the effect of temperature in the reduction of iminium intermediate (Formula VI) by the reducing agent Formula XXXII. Lowering the reduction temperature to -40°C (Procedure K(ii) Example 9) resulted in an increase in both the ratio of 1,4-reduction production, enamine (VIII), versus 1,2-reduction product, 3,4-dehydrovinblastine (VII), (4.2:1), as well as the overall yield of the reaction (85%).

The second area of improvement relates to the oxidative transformation of the enamine (Formula VIII) to the iminium intermediate (Formula XVI).

Various parameters for this oxidative transformation have been studied to optimize the yield of vinblastine (Formula I) production.

Table 4 indicates the effect of ferric chloride concentration. Two equivalents of ferric chloride provide the highest yield of vinblastine (I).

Table 1. NADH Models for 1,2-Versus 1,4-Reduction of Iminium Intermediate VI.



Formula	Reducing Agents	Procedure	Reducing Agents	Procedure	Formula
					B
XXVII	$R' = \text{---CH}_2\text{C}_6\text{H}_5$	A			D
XXVIII	$= \text{---CH}(\text{C}_6\text{H}_5)_2$	C			
	$= \text{---CH}(\text{CO}_2\text{Me})$				
XXIX	$= \text{---CH}(\text{OR}'')$	F			E
	$= \text{---CH}(\text{OR}'')$	G			
	$R'' = \text{Ac}$				
XXX	$= \text{---CH}(\text{OMe})$	H			
XXXI	$= \text{---CH}(\text{CO}_2\text{Me})$	I			
XXXII	$= \text{---CH}(\text{CO}_2^-\text{Na}^+)$	J, K			

Table 2. Effect of Reducing Agent on 1,4- vs. 1,2-Reduction of Iminium VI

Reduction Procedure ^{1,4}	1,4:1,2-Reduction Products ²	Yield ³ (%)
A ⁵	1:1	75
B ⁵	1:1	60
C	0.9:1.0	60
D	1:1	40
E	1.1:1	60
F	2:1	65
G	1.5:1	70
H	1.1:1	65
I	2.3:1	70
J	2.2:1	70

1 Typical Procedure: 100 mg Iminium VI in 6 ml methanol to which reducing agents C-J (1-6 eq.) dissolved in 6 ml methanol were added. Full details in Experimental Section.

2 By reverse phase HPLC quantitation.

3 Combined 1,2-reduction (3,4-dehydrovinblastine, VII) + 1,4-reduction (enamine VIII) products.

4 All of these reactions were conducted at 20° C.

5 Procedures A and B are presented in Canadian application Serial No. 527,897 and presented here for comparison.

Table 3. Effect of Temperature on 1,4- vs. 1,2-Reduction of Iminium VI.

Reduction Procedure ¹	Temp. (°C)	1,4:1,2-Reduction Products ²	Yield ³ (%)
D	20	2.2:1	70
K (I)	-20	3.2:1	80
K (II)	-40	4.2:1	85

1 Typical procedure as in Table 2.

2 Quantitation by HPLC.

3 Combined 1,2-reduction (3,4-dehydrovinblastine, VII) + 1,4-reduction (enamine VIII) products.

Table 4. Effect of Ferric Chloride on Production of Vinblastine (I) from Enamine VIII³

Amount of FeCl ₃ (Equivalents) ³	Oxidation Conditions (Temp., time)	Yield of Vinblastine ²
0	Air ¹ , 0° C, 5 min	0
1	Air ¹ , 0° C, 5 min	13.3
2	Air ¹ , 0° C, 5 min	19.0
3	Air ¹ , 0° C, 5 min	10.4

¹ At a rate of 60 ml/min.

² By reverse-phase HPLC quantitation, after reductive work-up with NaBH₄.

³ Enamine VIII generated at -40° C (Procedure K (11)).

Table 5. Effect of Time of Oxidation on Production of Vinblastine (I) from Enamine VIII³

Time ¹ (min)	% Yield of Vinblastine ²
1	8.2
5	15.4
10	15.5
15	15.7
45	6.5

¹ Reaction conditions: - 2 eq. ferric chloride added, air bubbled through the solution at 60 ml/min at 0° C.

² By reverse-phase HPLC quantitation after reductive work-up with NaBH₄.

³ Enamine VIII generated at -40° C (Procedure K (11)).

Table 6. Effect of Oxidation Temperature on Production of Vinblastine (I)
from Enamine VIII³

Temp., ° C ¹	% Yield of vinblastine ²
-40	3.7
-23	6.2
0	19.6
20	20.6
45	16.0

¹ Reaction conditions: 2 eq. ferric chloride added, air bubbled through the solution at 60 ml/min for 15 min.

² By reverse-phase HPLC quantitation after reductive work-up with NaBH₄.

³ Enamine generated at -40° C (Procedure K (ii)).

Table 7. Effect of Dilution on Production of Vinblastine (I) from Enamine VIII³.

Dilution Factor ^{1,4}	% Yield of Vinblastine ²
1	19.6
5	25.2
10	30.1
20	29.6
50	24.7

- ¹ Reaction conditions: 2 eq. ferric chloride added, air bubbled through the solution at 60 ml/min for 15 min. at 0° C.
- ² By reverse-phase HPLC quantitation after reductive work-up with NaBH₄.
- ³ Enamine generated at -40° C (Procedure K (ii)).
- ⁴ Dilution Factor 1 - 100 mg Iminium VI in 6 ml methanol to which reducing agent Formula XXXII (6 eq.) in 6 ml methanol was added. (Total volume - 12 ml) Dilution Factor 5 - Total volume of 60 ml, etc.

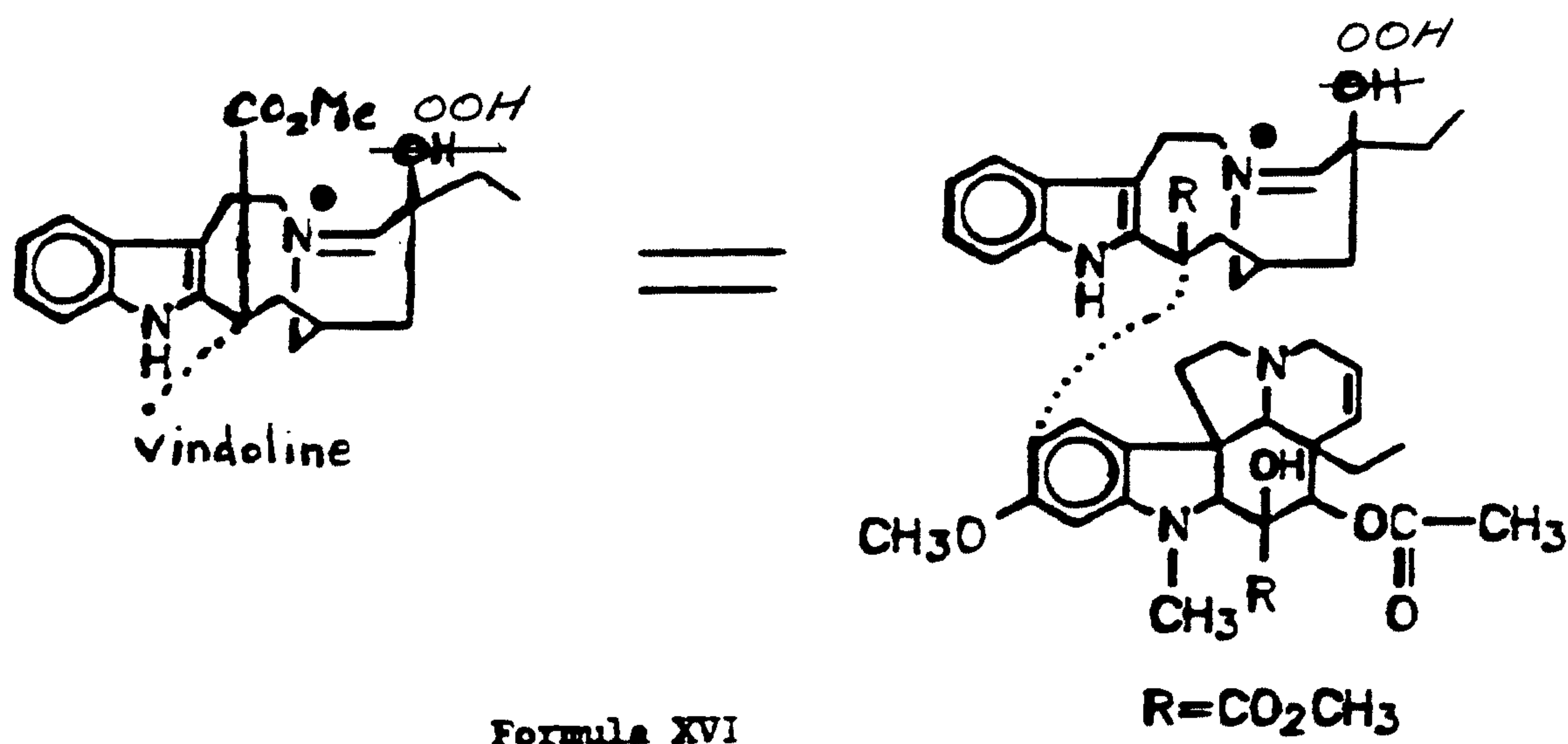
Table 5 indicates results relating to yield of vinblastine versus time of oxidation. The maximum yield of vinblastine (I) is reached after 5 to 20 minutes of aeration in the presence of 2 equivalents of ferric chloride.

Table 6 shows the results of various oxidation temperatures, in the presence of two equivalents of ferric chloride, on the yield of vinblastine (I). The temperature range of 0°C to 20°C provides the highest yield of vinblastine (I) after a reductive work-up with NaBH_4 , as quantified by reverse-phase HPLC.

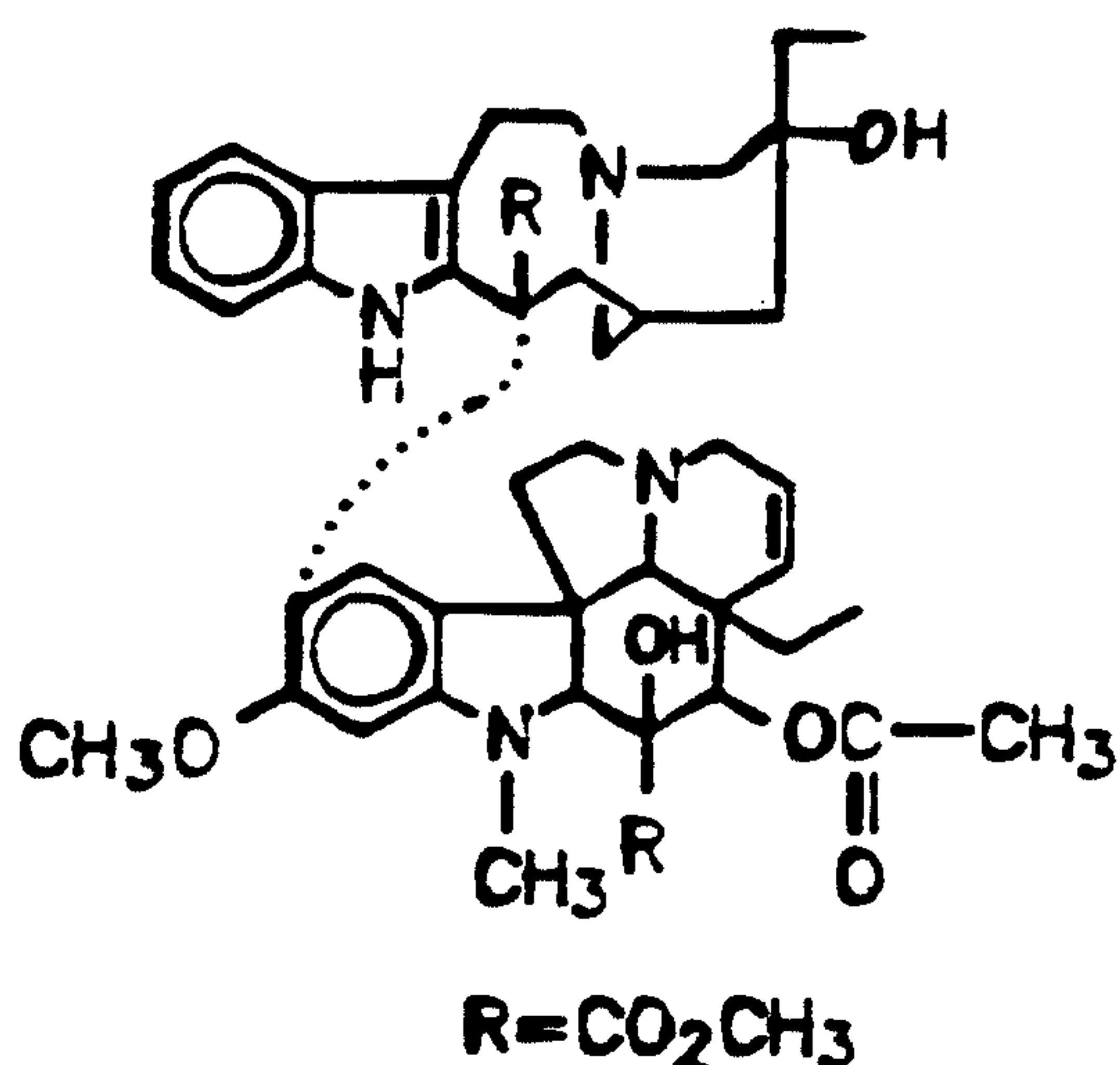
The effect of dilution of the enamine (VIII) solution on the production of vinblastine (I), is indicated in Table 7. A dilution factor of 10 to 20 on the enamine (VIII) solution before aeration in the presence of ferric chloride (2 equivalents) at 0°C, affords the best yield of vinblastine (I) as quantified by reverse-phase HPLC after reductive work-up with NaBH_4 .

In summary, the specific improvements in the present application as they relate to the oxidative transformation of the enamine (VIII), involve the dilution (5 to 50 folds) of the enamine (Formula VIII) solution, obtained in the above reduction of iminium intermediate (Formula VI), by the same solvent used in the reduction. For practical purposes, the preferred dilution factor is usually in the range of 8 to 12 folds. The above procedure is conducted at a low temperature (0°C to -70°C), preferably below -40°C and under cover with inert conditions such as argon or an inert gas of Group Zero of the Periodic Table (nitrogen, helium, neon, etc.). After this dilution

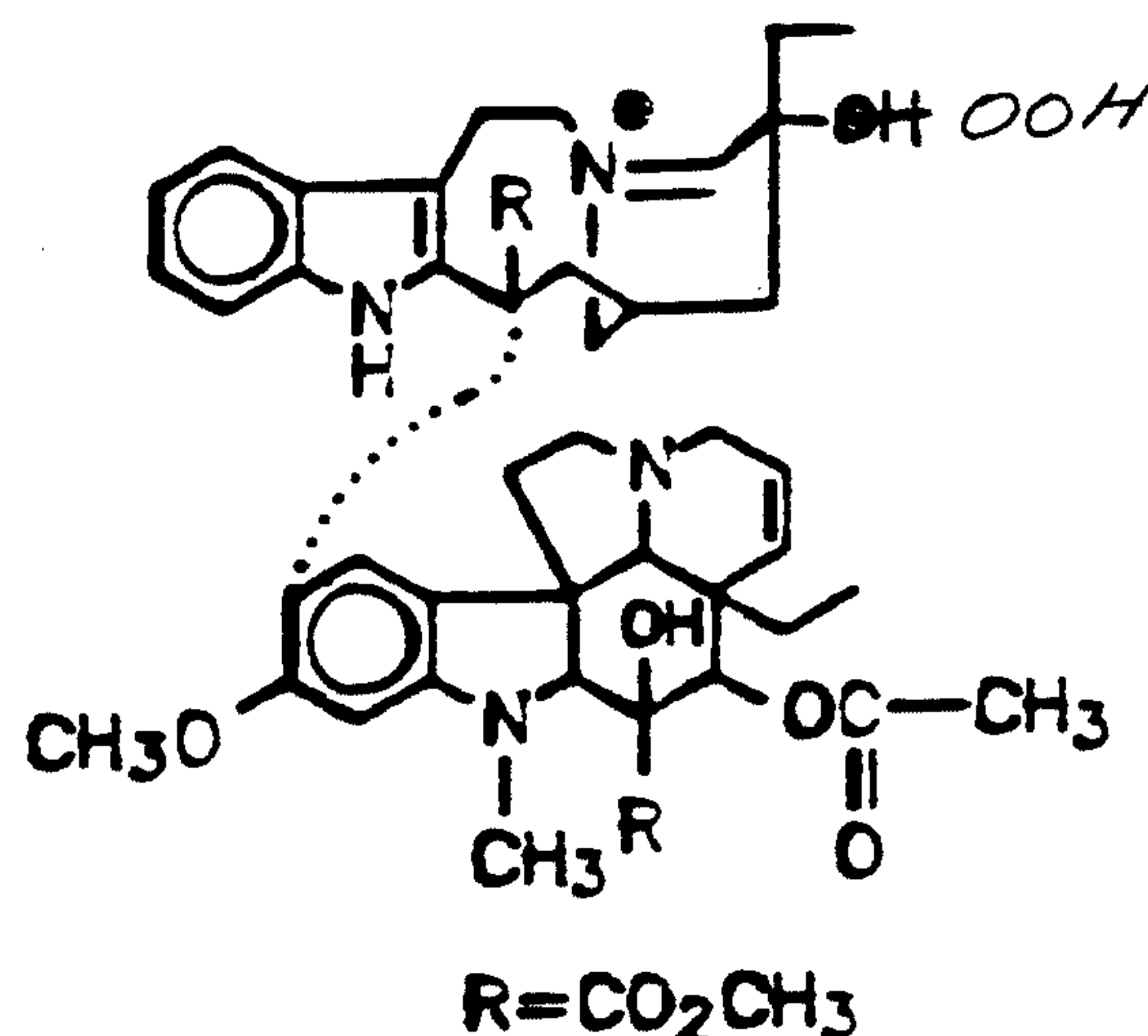
process, the oxidative transformation of the enamine (Formula VIII) can be carried out as described above (aeration at 60 ml/min for 15 min at 0°C in the presence of ferric chloride (2 eq.)) to afford the corresponding iminium intermediates (Formula XVI).



The third area of improvement relates to the reduction of iminium intermediates (Formula XVI) by alkali metal borohydride (NaBH_4 , KBH_4 , LiBH_4 , etc.) to vinblastine (Formula I) and/or leurosidine (Formula XXXV). The iminium intermediates (Formula XVI and Formula XVIa) produced from the oxidative transformation of enamine (Formula VIII) are reduced by the addition of alkali metal borohydride at low temperature (4°C to -20°C), preferably at 0°C. The reduction is conducted at pH lower than 8.5 and preferably at 7.5 to 8. The total reaction mixture is then concentrated in vacuo at low temperature (0°C to 10°C) before extraction and isolation of alkaloid products.



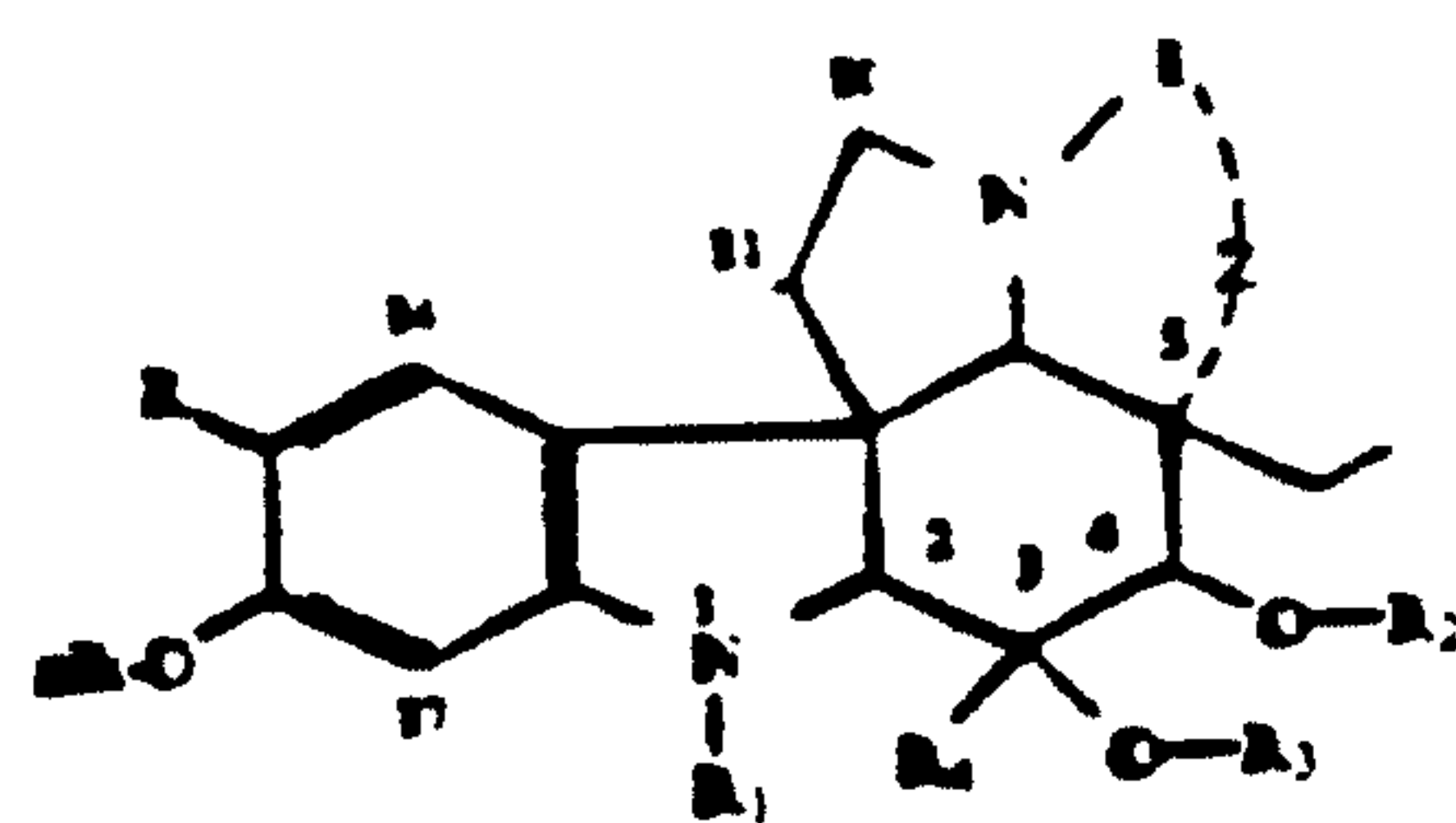
Formula XXXV (Leurosidine)



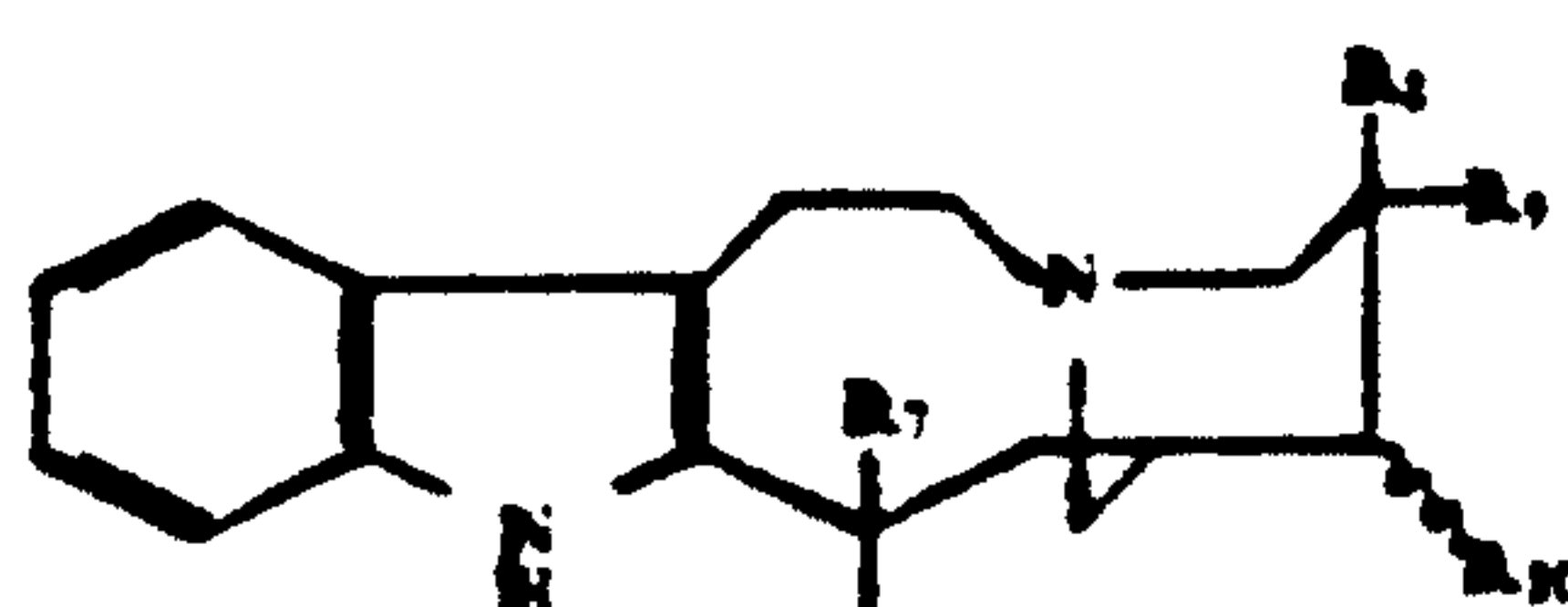
Formula XVIa

For practical purposes, all the above improvements can be incorporated, as indicated, directly into the overall process conducted in a one-pot operation from the indole unit (Formulas II, XXII or XXIII) and the dihydroindole unit (Formula XXI, $R = H$) to the final products of Formula XXI. Isolation of the various intermediates (Formulas XXIV, VI, VIII and XVI) is omitted as summarized in Scheme 1.

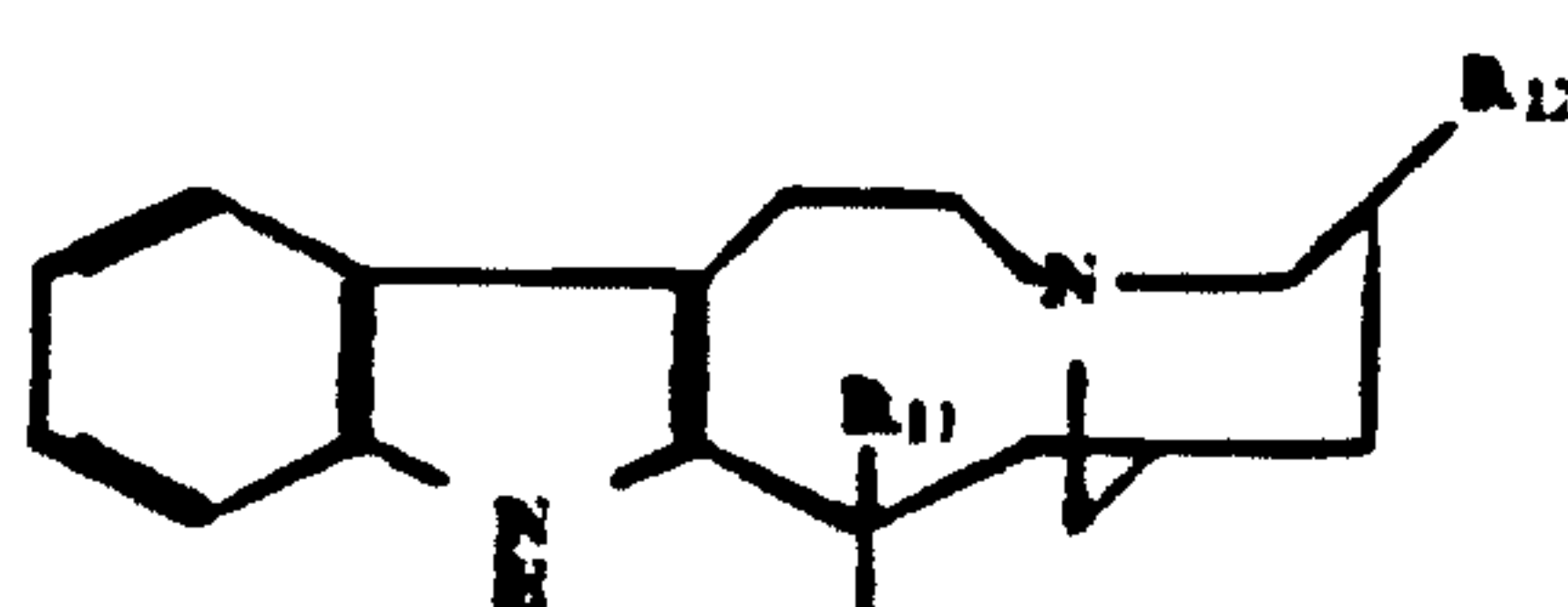
In summary, the present method is applicable to the production of dimer products from catharanthine and dihydrocatharanthine with vindoline as starting materials and phenyl, alkyl and amide derivatives embraced by the following formulas:



XXI

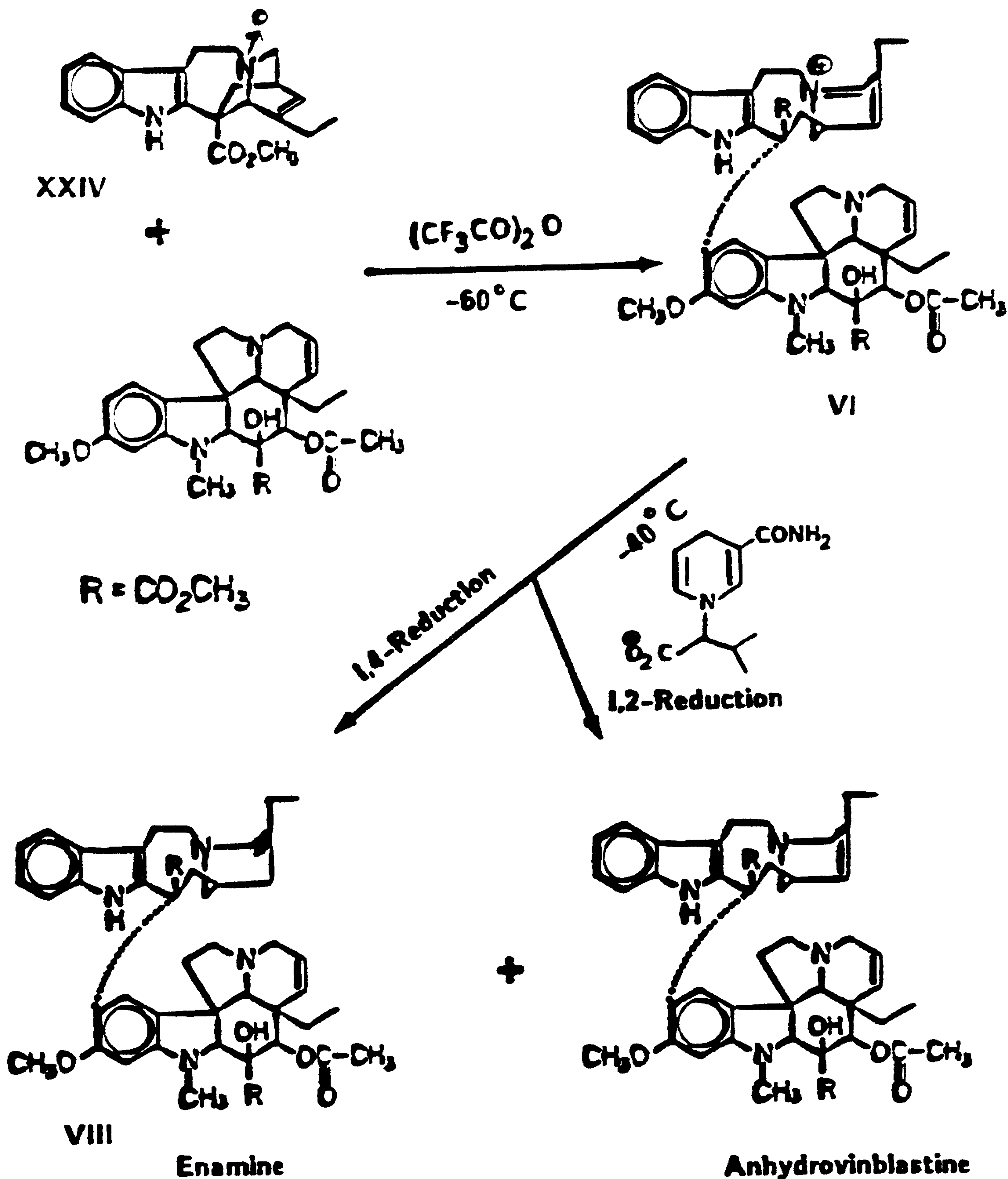


XXII

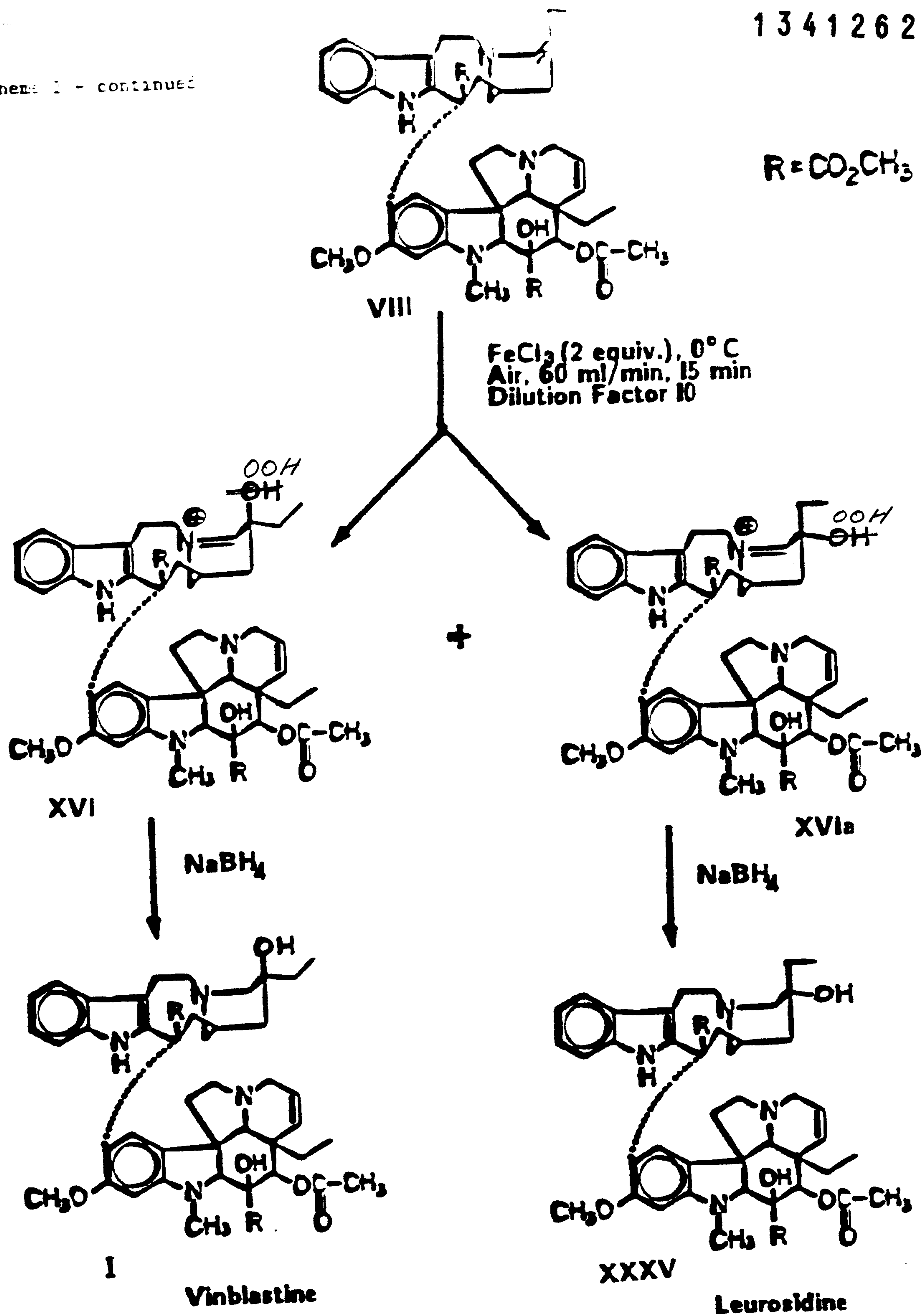


XXIII

Scheme 1. Optimum procedure for one-pot process - vinblastine from catharanthine and vindoline.



Scheme 1 - continued

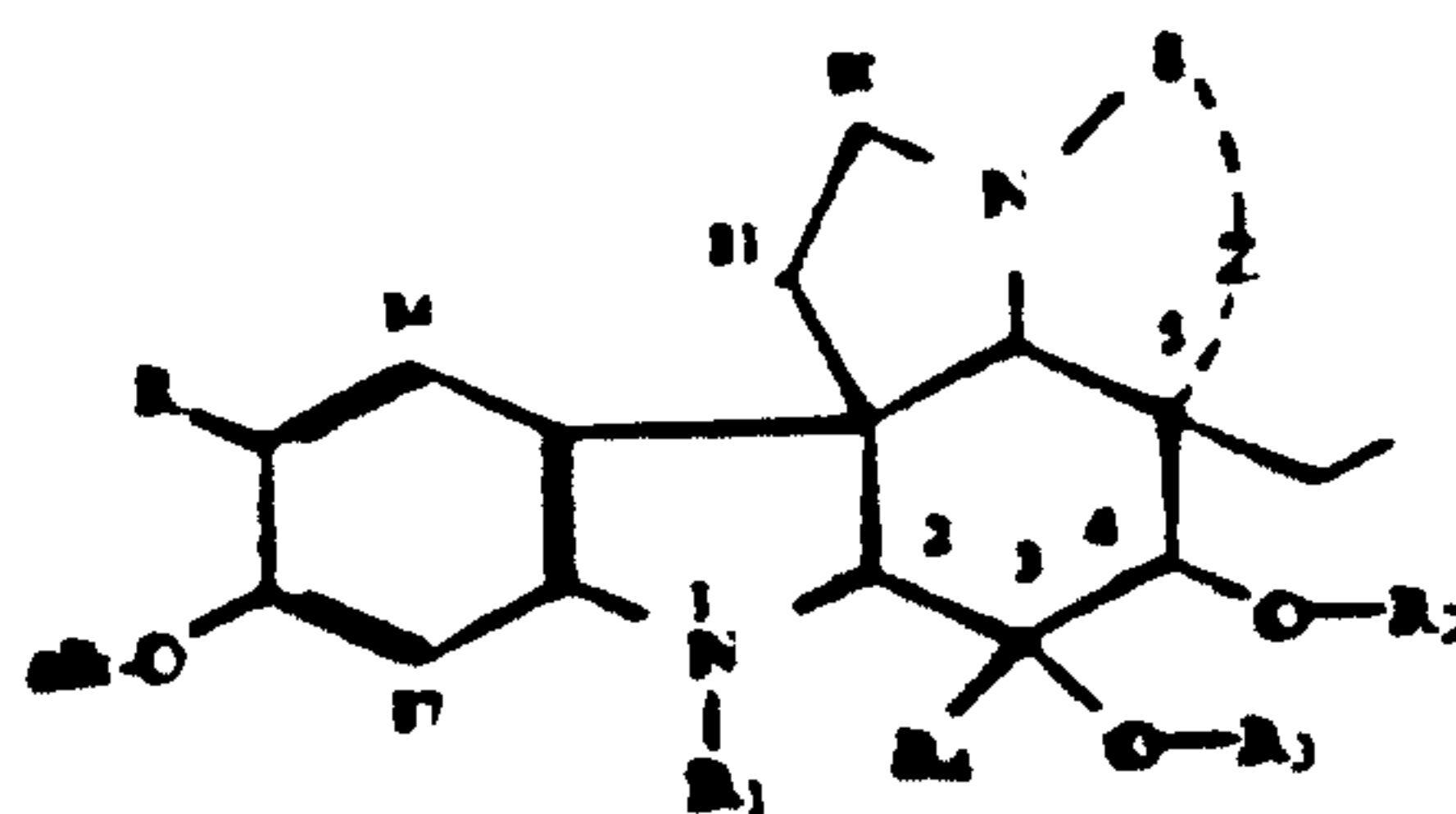


Overall Yield: Vinblastine (42%); Leurosidine (17%); Anhydrovinblastine (18%)

Formula XXI is as pictured and in that formula alk represents a lower alkyl group of C_1-C_6 and preferably C_1-C_3 ; aryl is mono-aryl such as benzyl, styryl, and xylyl; R_1 is a member of the group consisting of hydrogen, alk, CHO and COR_5 where R_5 is alkyl or aryl; R_2 and R_3 are members of the group consisting of hydrogen and $-CO-alk$; R_4 is a member of the group consisting of $COO-alk$, $CONH-NH_2$, $CONH_2$, $CONHR_6$, and $CON(R_6)_2$ where R_6 is alkyl; Z is a member of the group consisting of $-CH_2-CH_2-$ and $-CH-CH-$ and R is a member of the indole family represented by Formula XXII where R_7 is a member of the group consisting of hydrogen, or $COO-alk$; R_8 is a member of the group consisting of hydrogen, OH, O-alk, OCO-alk or alkyl; R_9 is a member of the group consisting of hydrogen, OH, O-alk, OCO-alk, or alk; R_{10} is a member of the group consisting of hydrogen, OH, O-alk, OCO-alk, or alk, or Formula XXIII where R_{11} is a member of the group consisting of hydrogen or $COO-alk$; R_{12} is a member consisting of alkyl.

Specific Description of the Invention

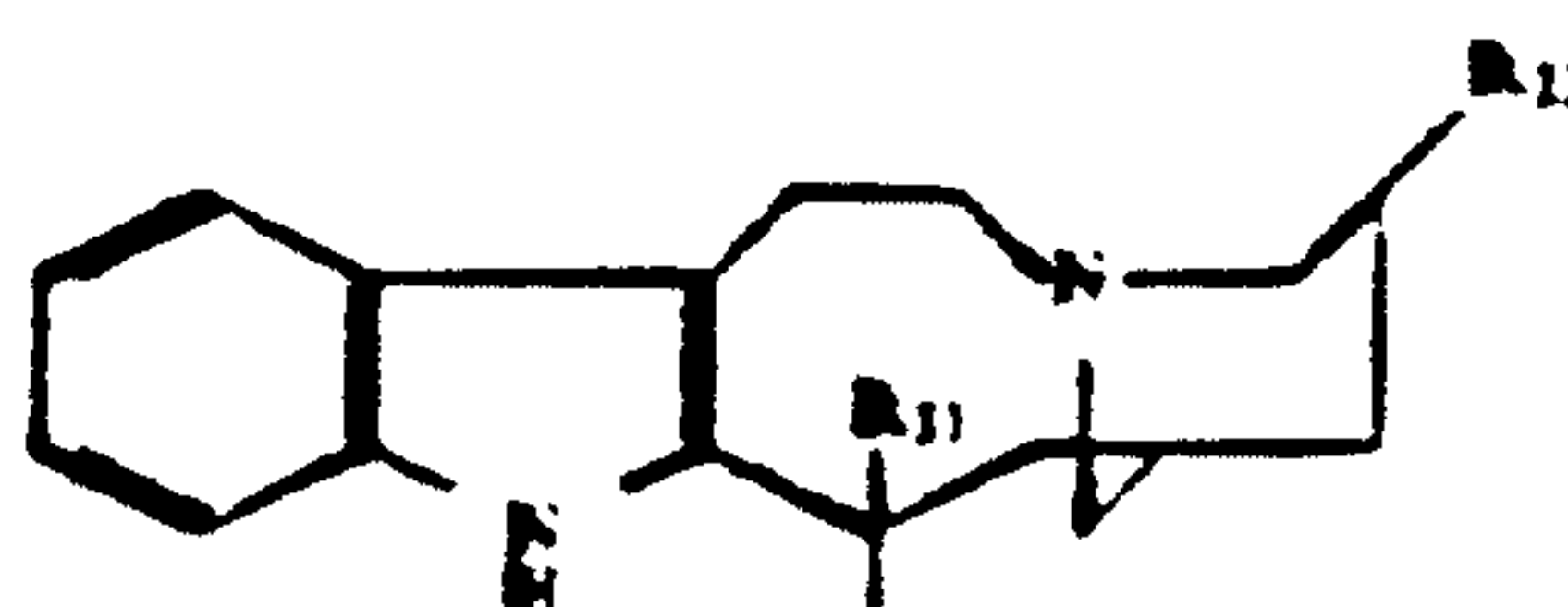
This invention is specifically a process for the production of compounds represented by the following formulas:



XXI



XII



XXIII

wherein in Formula XXI

Alkyl = CH_3 or $(\text{CH}_2)_n\text{XH}_3$ where $n=1-5$

R_1 = CH_3 or CHO

R_2 = H or CO-alk

R_3 = H

R_4 = COO-alk or $\text{CONR}_{13}\text{R}_{14}$ where R_{13} and R_{14} can be any member of the group consisting of hydrogen, alkyl, substituted alkyl, aryl or substituted aryl functions

Z = $-\text{CH}=\text{CH}-$ or $-\text{CH}_2-\text{CH}_2-$

R = Formula XXII or XXIII

R_7 = H or COO-alk

R_8 = H , OH , O-alk , OCO-alk or alkyl

R_9 = H , OH , O-alk , OCO-alk or alkyl

R_{10} = H , OH , O-alk , OCO-alk

R_{11} = H or COO-alk

R_{12} = H or alkyl

wherein the process is for the synthesis of a dimer derived from an indole unit of the natural Iboga alkaloid family containing an aza bicyclo-octane portion and a dihydroindole

unit of the natural Aspidosperma and Vinca alkaloid families, the stereochemistry of the carbon-carbon linkage between these two units being identical with that of vinblastine which consists of

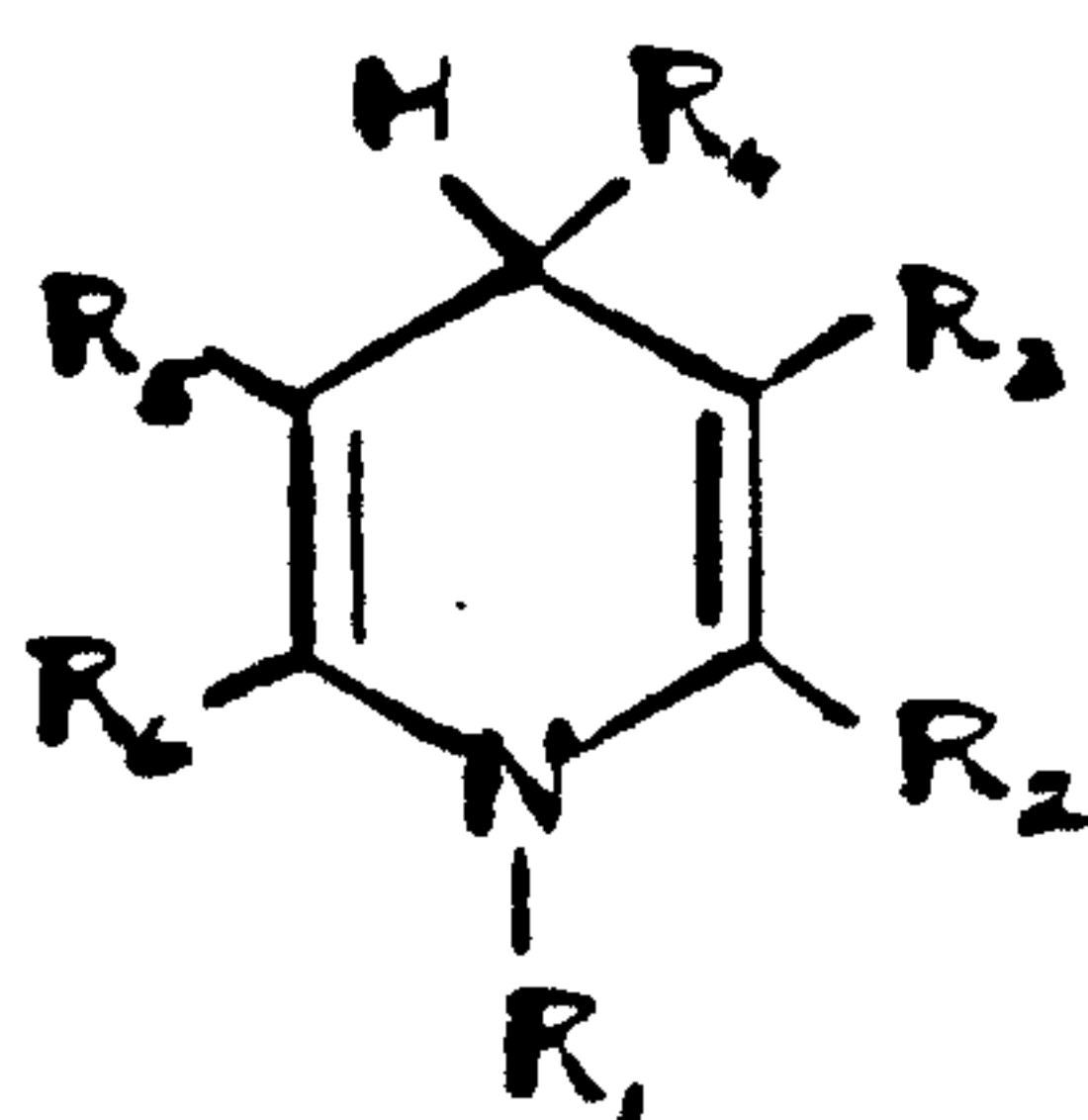
(a) forming an N-oxide intermediate in the cold at a temperature of -70°C to $+40^{\circ}\text{C}$ from said indole unit by oxidizing the bridge nitrogen and without isolating said intermediate;

(b) treating said N-oxide indole intermediate in the presence of one member of the group consisting of acetic anhydride, halogenated acetic anhydride, and acetyl chloride to effect a Polonovski-type fragmentation reaction;

(c) without isolating the product of step (b), coupling said reaction product with a dihydroindole unit in the presence of acetic anhydride, halogenated acetic anhydride, and acetyl chloride at a low temperature of about -70°C to $+40^{\circ}\text{C}$ under inert conditions;

(d) the product of step (c) is isolated by solvent evaporation preferably at low temperature in the range of -20°C to 0°C ;

(e) the product of step (d) is reduced by 1,4-dihydropyridine compounds represented by Formula IX



IX

where R_3 and R_5 in Formula IX are carboxylic esters (COO-alk) and R_1 , R_2 , R_4 and R_6 are members of the group

consisting of H, alkyl, aryl (Hantzsch ester series) or N-substituted 1,4-dihydronicotinamides where R_1 is a substituted alkyl or substituted aryl function, for example, benzyl, and R_3 is CONR_7R_8 where R_7 and R_8 is one member of the group consisting of hydrogen, alkyl or aryl function;

(f) the product of step (e), an enamine, Formula VIII, is isolated by solvent evaporation, preferably at low temperature in the range of -20°C to 0°C ;

(g) the product of step (e), a solution of enamine VIII, is diluted (5 to 50 folds) by the same solvent employed, preferably in the range of 8 to 12 folds at a low temperature (0°C to -70°C), preferably below -40°C ;

(h) the enamine obtained in step (f) or the enamine solution obtained in step (g) is used to prepare iminium intermediates, Formula XVI or XVIa, by a number of oxidative processes including:

(1) controlled aeration/oxygenation in which a solution of the enamine is stirred in open air or with a stream of air/oxygen bubbled through the solution;

(2) as in (1) but with the addition of a metal ion;

(3) as in (1) but with the addition of a flavin coenzyme, as represented by Formula XII, to generate, in situ, the corresponding 1,5-dihydroflavin coenzyme, as represented by Formula XIII;

(4) as in (1) but with the addition of hydrogen peroxide and/or hydroperoxides as represented by the Formula R-OOH where R is alkyl or aryl

(i) the product, an iminium intermediate or

iminium intermediates obtained in step (h) is isolated by solvent evaporation, preferably at low temperature in the range of -20°C to 0°C ;

(j) the product obtained in step (i) or the iminium intermediate solution obtained in step (h) is converted to the target compounds of Formula XXI, for which vinblastine and vincristine are examples and leurosidine (Formula XXXV) by reduction with alkali metal borohydride (NaBH_4 , KBH_4 , LiBH_4) in suitable solvents (organic and/or aqueous) as used in the oxidative processes of step (h).

Of special importance is the presence of electron rich functional groups (e.g., carboxylic esters and carboxylate salts) in R_1 of Formula IX, capable of coordination with the positively charged iminium intermediate (Formula VI). Some examples of these 1,4-dihydropyridine compounds are given in Table 1 (e.g., Formulas XXXI and XXXII). Such coordination increases both the regioselectivity (1,4-reduction over 1,2-reduction) and the rate of the reduction of iminium intermediate (Formula VI), leading to an improved yield of the enamine (Formula VIII).

The reduction is conducted under an inert atmosphere at -60°C to $+60^{\circ}\text{C}$ but preferably in the temperature range -20°C to -40°C . The solvents employed are alcohols, acetonitrile or higher members of this series, dimethyl sulfoxide, dimethylformamide, various ethers such as dioxane and tetrahydrofuran, and chlorinated hydrocarbons.

The oxidative processes in step (h) (1)-(4) are

conducted in organic solvents such as alcohols, acetonitrile or higher members of this series, dimethyl sulfoxide, dimethylformamide, various ethers such as dioxane, tetrahydrofuran, aromatic hydrocarbons such as benzene, toluene, etc. An aqueous buffer (e.g., phosphate, Tris-HCl, MES buffers) at pH 5-9, but preferably in the range of 6-8, can be used as co-solvent. The reaction temperature may vary from -60°C to $+60^{\circ}\text{C}$.

Of special importance is the presence of electron rich functional groups (e.g., carboxylic esters and carboxylate salts) in R_1 of Formula IX, capable of coordination with the positively charged iminium intermediate (Formula VI). Some examples of these 1,4-dihydropyridine compounds are given in Table 1 (e.g., Formulas XXXI and XXXII). Such coordination increases both the regioselectivity (1,4-reduction over 1,2-reduction) and the rate of the reduction of iminium intermediate (Formula VI), leading to an improved yield of the enamine (Formula VIII).

The reduction is conducted under an inert atmosphere at -60°C to $+60^{\circ}\text{C}$, but preferably in the temperature range of -20°C to -40°C . The solvents employed are alcohols, acetonitrile or higher members of this series, dimethyl sulfoxide, dimethylformamide, various ethers such as dioxane and tetrahydrofuran and chlorinated hydrocarbons.

The product of step (e) above, an enamine, Formula VIII, is isolated by solvent evaporation, preferably at low temperature in the range of -20°C to 0°C .

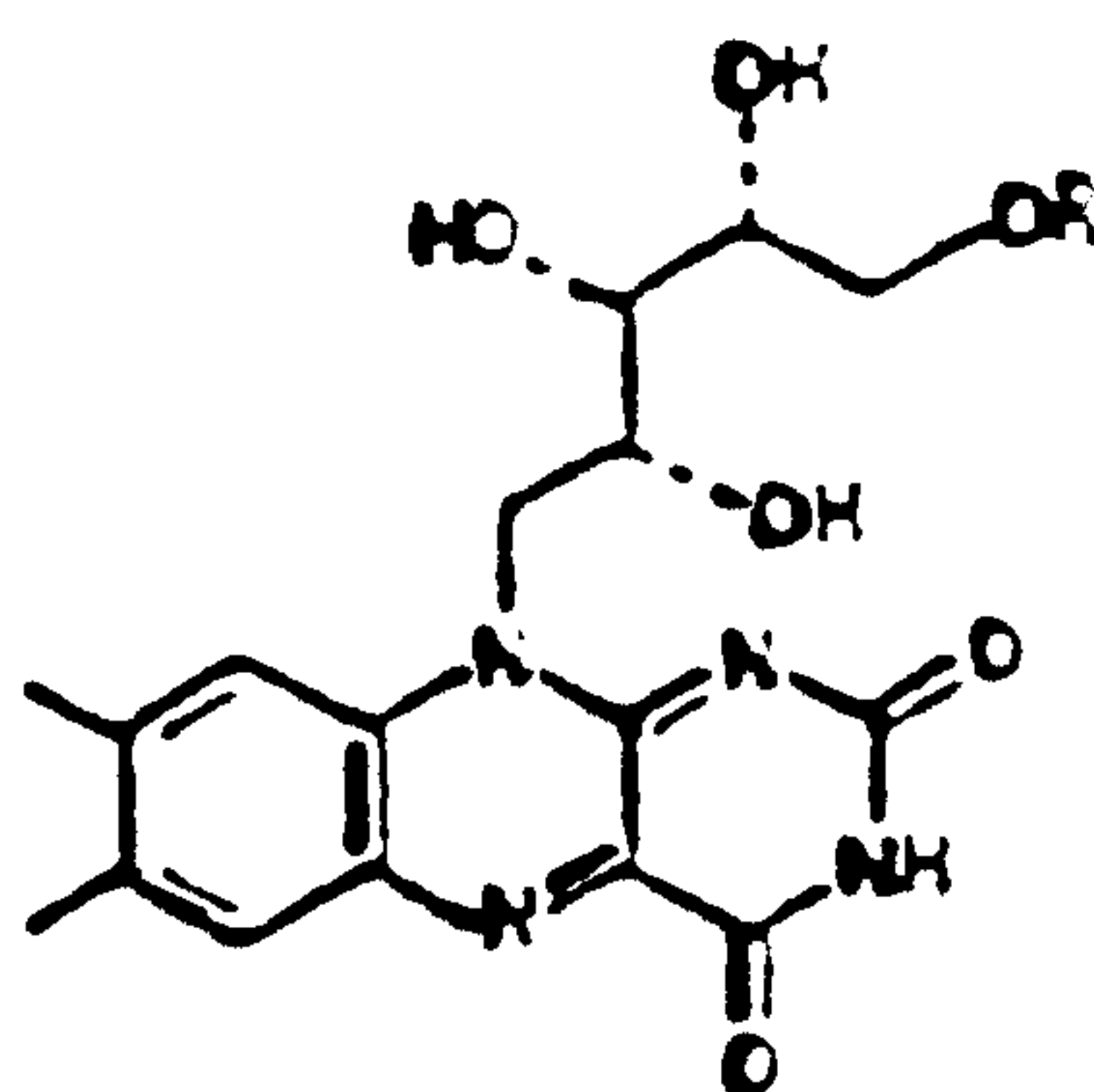
The process of this invention also prepares an

enamine and oxidizes said enamine to the iminium intermediate (Formula XVI and XVIa) by a number of oxidative processes including:

(a) controlled aeration/oxygenation in which a solution of the enamine is stirred in open air with a stream of air/oxygen bubbled through the solution;

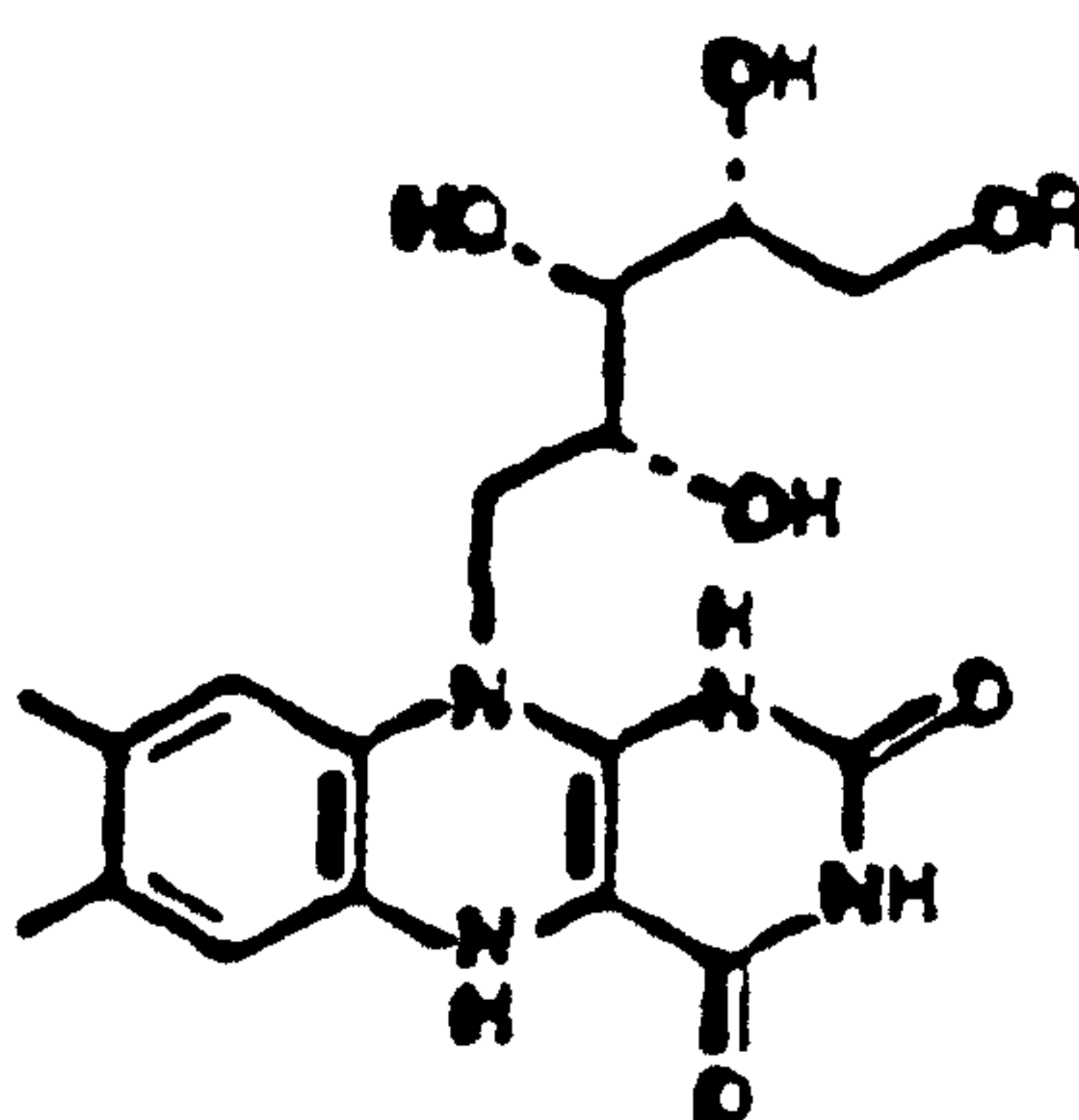
(b) as in step (h)(1) but with the addition of a ferric chloride;

(c) as in step (h)(1) but with the addition of a flavin coenzyme, as represented by Formula XII:



XII

to generate, in situ, the corresponding 1,5-dihydroflavin coenzyme, as represented by Formula XIII



XIII

The oxidative processes are conducted in organic solvents such as alcohols, acetonitrile or higher members of

this series, dimethyl sulfoxide, dimethylformamide, ethers such as dioxane, tetrahydrofuran, aromatic hydrocarbons such as benzene, toluene, etc.

EXAMPLES

The following examples (Examples 1 - 8) were conducted at 20°C.

Example 1

Reduction of Iminium Intermediate (Formula VI) with 1-Diphenylmethyl (-1,4-dihydronicotinamide (Formula IX, R_1 = diphenyl methyl; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXVII) - Synthesis of Enamine (Formula VIII) - Procedure C)

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed ethanol (6 ml) was added 1-diphenylmethyl-1,4-dihydronicotinamide (Formula XXVII) (76 mg, 2.5 equivalents) in methanol (6 ml) under a positive atmosphere of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 60 min. After this, reverse phase HPLC analysis (Waters Radial-Pak C_{18} or CN cartridge, methanol- H_2O - Et_3N as solvent system) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 0.9:1 (60% yield).

Example 2

Reduction of Iminium Intermediate (Formula VI) with 1-Benzyl-3-cyano-1,4-dihydropyridine (Formula IX, R_1 = benzyl; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CN$) (Formula XXXIII) - Synthesis of Enamine (Formula VIII) - (Procedure D).

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1-benzyl-3-cyano-1,4-dihydropyridine (Formula XXXIII) (206 mg, 10 equivalents) in methanol (10 ml) under a positive atmosphere of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 60 min. After this, reverse phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 1:1 (40% yield).

Example 3

Reduction of Iminium Intermediate (Formula VI) with 1-Benzyl-1,4-dihydronicotinyl-(2'-carbamoyl-pyrrolidinyl)-amide (Formula IX, R_1 = benzyl; $R_2 = R_4 = R_5 = R_6 = H$; R_3 = (2' carbamoyl-pyrrolidinyl) carbonyl) (Formula XXXIV) - Synthesis of Enamine VIII) - (Procedure E).

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1-benzyl-1,4-dihydronicotinyl-(2'-carbamoyl-pyrrolidinyl)-amide (Formula XXXIV) (163 mg, 5 equivalents) in methanol (5 ml) under a positive pressure of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 30 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 1.1:1 (60% yield).

Example 4

Reduction of Iminium Intermediate (Formula VI) with 1,4-Dihydro-1-(1-methoxycarbonyl isobutyl)-nicotinamide (Formula

IX, R_1 = 1-methoxycarbonyl isobutyl; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXVIII) - Synthesis of Enamine (Formula VIII) - (Procedure F)

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1,4-dihydro-1-(1-methoxy carbonylisobutyl)-nicotinamide (Formula XXVIII) (150 mg, 6 equivalents) in methanol (6 ml) under a positive pressure of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 30 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 2:1 (65% yield).

Example 5

Reduction of Iminium Intermediate (Formula VI) with 1-(2',3',4',6'-Tetraacetyl-(beta)-D-glucopyranosidyl)-1,4-dihydronicotinamide (Formula IX, R_1 = (2',3',4',6'-Tetraacetyl-(beta)-D-glucopyranosidyl; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXIX) - Synthesis of Enamine (Formula VIII) - (Procedure G)

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1-(2',3',4',6'-tetra-acetyl-(beta)-D-glycopyranosidyl)-1,4-dihydronicotinamide (Formula XXIX) (238 mg, 5 equivalents) in methanol (10 ml) under a positive atmosphere of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 60 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of

1.5:1 (70% yield).

Example 6

Reduction of Iminium Intermediate (Formula VI) with 1,4-Dihydro-1-(2'-methoxycarbonyl isopropyl)-nicotinamide (Formula IX, $R_1 = 2'$ -methoxy carbonylisopropyl; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXX) - Synthesis of Enamine (Formula VIII) - (Procedure H)

To a stirred solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1,4-dihydro-1-(2'-methoxy-carbonylisopropyl)-nicotinamide (Formula XXX) (82 mg, 3.5 equivalents) in methanol (7 ml) under a positive atmosphere of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 30 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 1.1:1 (65% yield).

Example 7

Reduction of Iminium Intermediate (Formula VI) with 1,4-Dihydro-1-(1',2'-dimethoxy carbonyl ethyl 1, $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXXI) - Synthesis of Enamine (Formula VIII) - Procedure I)

To a solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1,4-dihydro-1-(1',2'-dimethoxy carbonyl ethyl)-nicotinamide (Formula XXXI) (148 mg, 5 equivalents) in methanol (10 ml) under a positive atmosphere of argon, the reducing agent being added

portionwise at the rate of 1 equivalent each 30 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 1.1:1 (70% yield).

Example 8

Reduction of Iminium Intermediate (Formula VI) with 1,4-Dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide (Formula IV, R_1 = sodium-isobutyl-1-carboxylate; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXXII) - Synthesis of Enamine (Formula VIII) - (Procedure J)

To a solution of iminium intermediate (VI, 100 mg) in degassed methanol (6 ml) was added 1,4-dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide (Formula XXXII) (130 mg, 5 equivalents) in methanol (6 ml) under a positive atmosphere of argon, the reducing agent being added portionwise at the rate of 1 equivalent each 30 min. After this, reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 2.2:1 (70% yield).

Example 9

Reduction of Iminium Intermediate (Formula VI) with 1,4-Dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide (Formula IX, R_1 = sodium-isobutyl-1-carboxylate; $R_2 = R_4 = R_5 = R_6 = H$; $R_3 = CONH_2$) (Formula XXXII) at low temperature - Synthesis of Enamine (Formula VIII) (Procedure K)

(i) To a solution of iminium intermediate (VI, 100

mg) in degassed methanol (6 ml) at -20°C was added 1,4-dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide (Formula XXXII) (155 mg, 6 equivalents) in methanol (6 ml) under a positive atmosphere of argon, the reducing agent being added in one portion. After 45 min. at this temperature reverse-phase HPLC analysis (as described above) indicated, among other products, formation of enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 3.2:1 (80% yield).

(ii) Carrying out the reaction above at -40°C gave, after 60 minutes, enamine (VIII) and 3',4'-dehydrovinblastine (VII) in a ratio of 4.2:1 (85% yield).

Example 10

Synthesis of Vinblastine (Formula I) by Oxidation of Enamine (Formula VIII) to Iminium Intermediate (Formula XVI) with Air in the Presence of Ferric Chloride at High Dilution. (Method 5)

The solution containing the enamine (VIII), (Procedure K (ii)) obtained from the iminium intermediate (VI, 200 mg) was diluted five-fold with methanol before oxidation (total vol.: 120 ml). Ferric chloride (75 mg, 2 equivalents) was then added, and air bubbled through the solution, at 0°C , for 20 min. Sodium borohydride (200 mg) was added, and the solution concentration in vacuo before adding water (100 ml) and extracting with ethyl acetate (3 x 200 ml). The combined organic extract was dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude product was purified by column chromatography (silica gel, TLC grade, 15 g). Elution with ether: chloroform (10:7) gave 3',4'-de-

hydrovinblastine (VII, 18 mg, 11%). Further elution with ether: chloroform: methanol (10:7:0.5) gave vinblastine (I, 62 mg, 37%).

Example 11

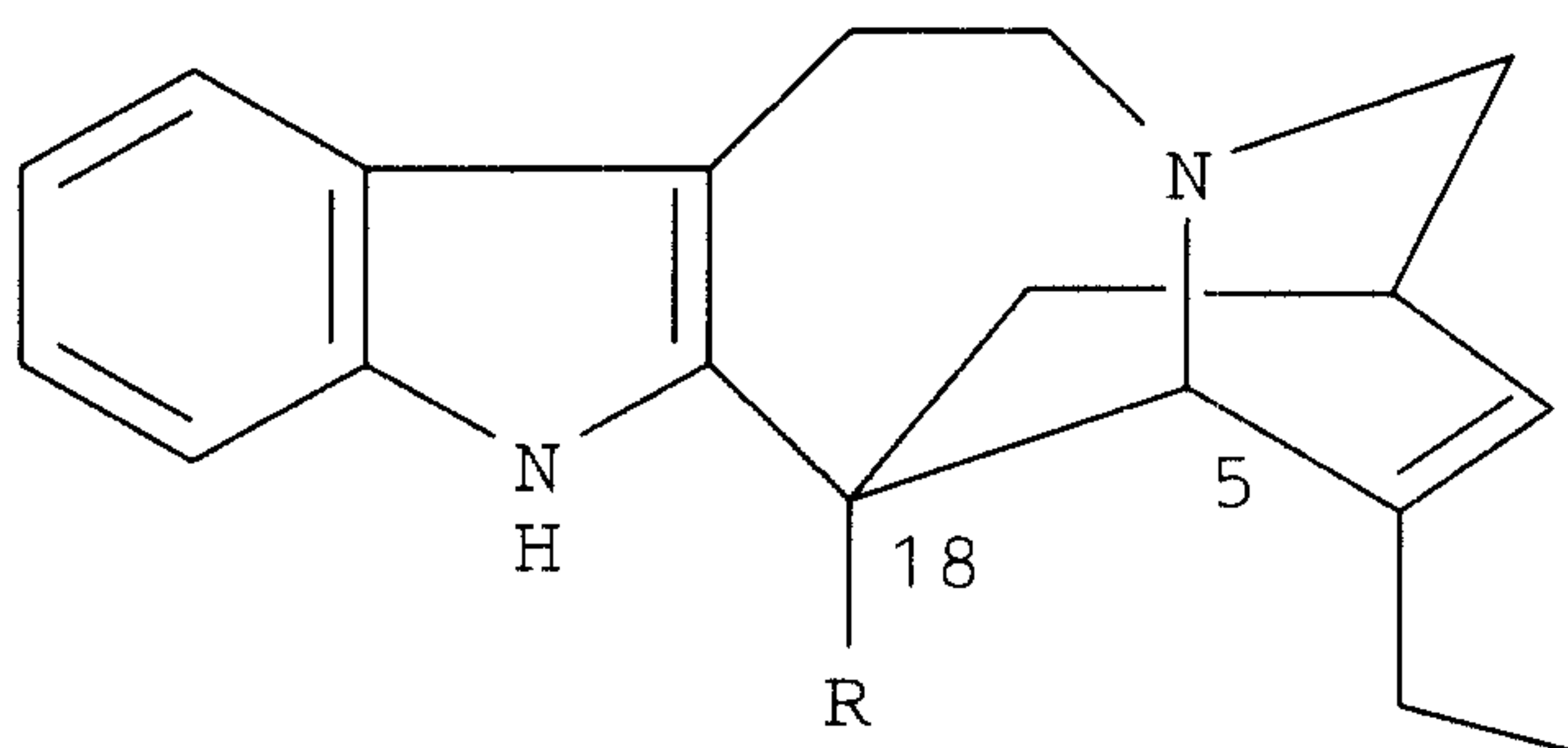
One-Pot Conversion of Catharanthine (Formula II) and Vindoline (Formula III) to Vinblastine (Formula I) and Leurosidine (Formula XXXV) - Overall Procedure

To a solution of catharanthine (II, 500 mg, 1.5 mmol) in dry dichloromethane (4.5 ml) at -15°C under a positive atmosphere of argon was added m-chloroperbenzoic acid (330 mg, 1.9 mmol) in one portion, and the mixture stirred at -10 to -15°C for 5 minutes. After this time the reaction mixture was cooled to -40°C and a solution of vindoline (III, 450 mg, 1 mmol) in dry dichloromethane (1 ml) was added, followed immediately by trifluoroacetic anhydride (1 ml, 7.1 mmol). After 2 h at -60°C volatiles were removed in vacuo (high vacuum pump) and dry, degassed methanol (12 ml) added after flushing the system with argon. The resulting orange solution was cooled to -40°C and a solution of 1,4-dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide (Formula XXXII) (1.5 g, 6 mmol) in dry degassed methanol (12 ml) was added under a positive atmosphere of argon. After reduction was complete (by reverse-phase HPLC monitoring), cold methanol (about 300 ml) was added, keeping the temperature of the solutionn between -5 and 0°C . Ferric chloride (330 mg, 2 mmol) was then added and dry air bubbled through the solution at a rate of 60 ml/min for a period of 20 min. Sodium borohydride (1 g) was added and the solution

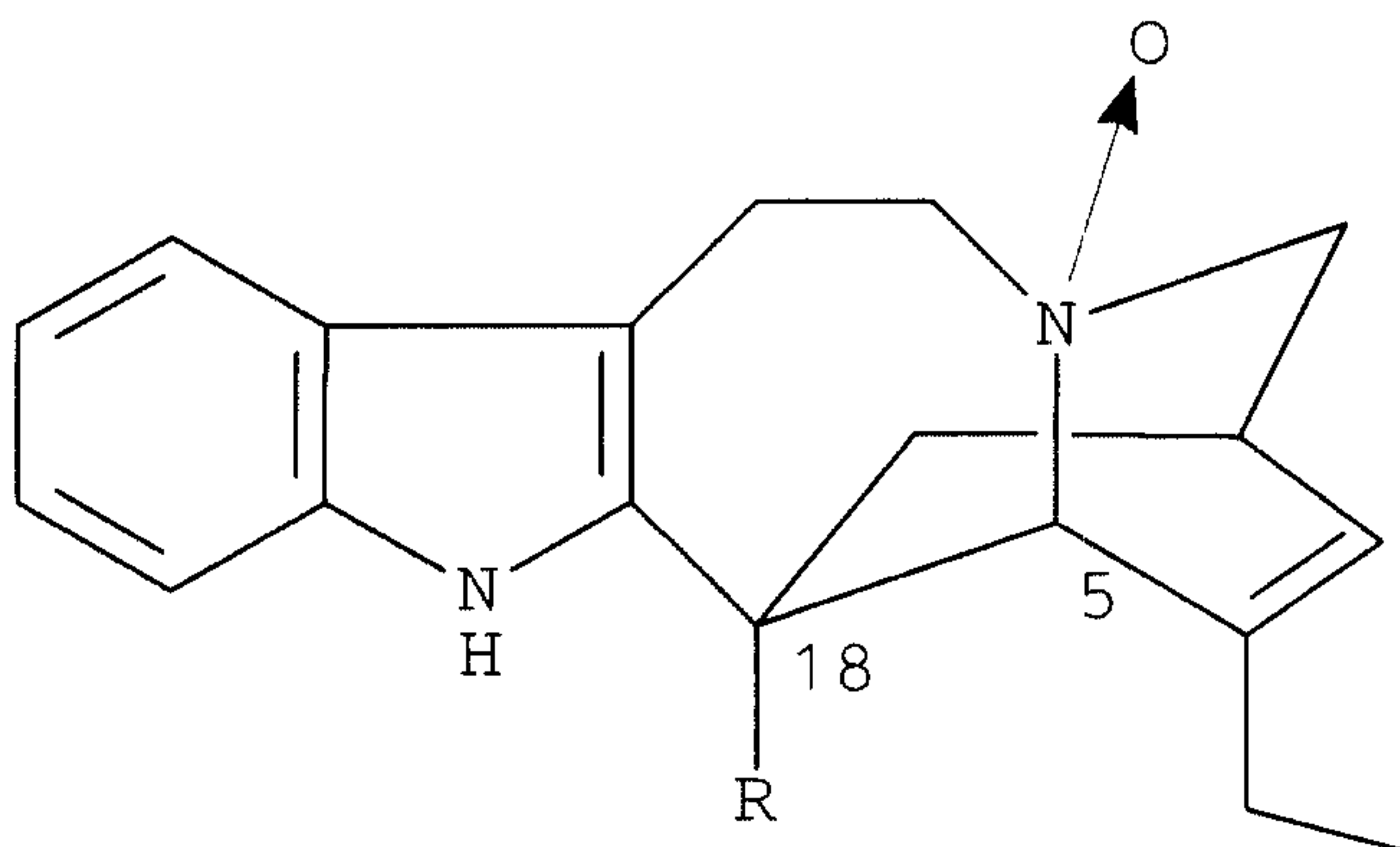
concentrated in vacuo (water aspirator) before adding water (100 ml) and extracting with ethyl acetate (3 X 150 ml). The combined organic extract was dried over Na_2SO_4 and the solvent evaporated in vacuo to give the crude product which was purified by chromatography as previously described to give 3',4'-dehydrovinblastine (VIII, 95 mg, 12%), vinblastine (I, 315 mg, 39%) and leurosidine (XXXV, 130 mg, 16%).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the production of dimer alkaloid compounds comprising the steps of:
 - (a) oxidizing an indole unit having a bridge nitrogen and being represented by the following formula:



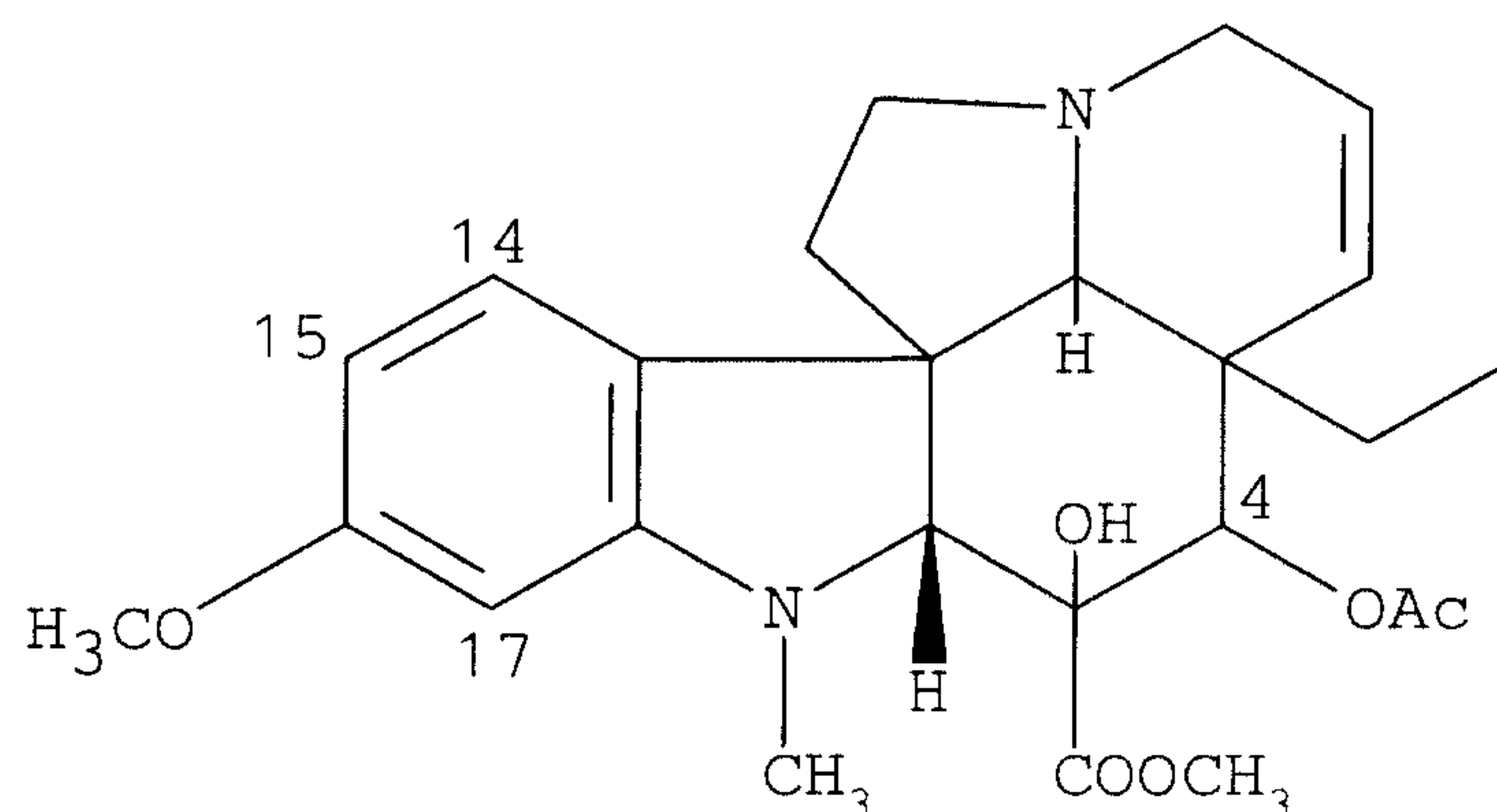
wherein R represents hydrogen or COO-alkyl, said oxidation being carried out in the cold, at a temperature from about -77 °C to about +40 °C, thereby oxidizing the bridge nitrogen of said indole unit and forming an N-oxide derivative as represented by the following formula:



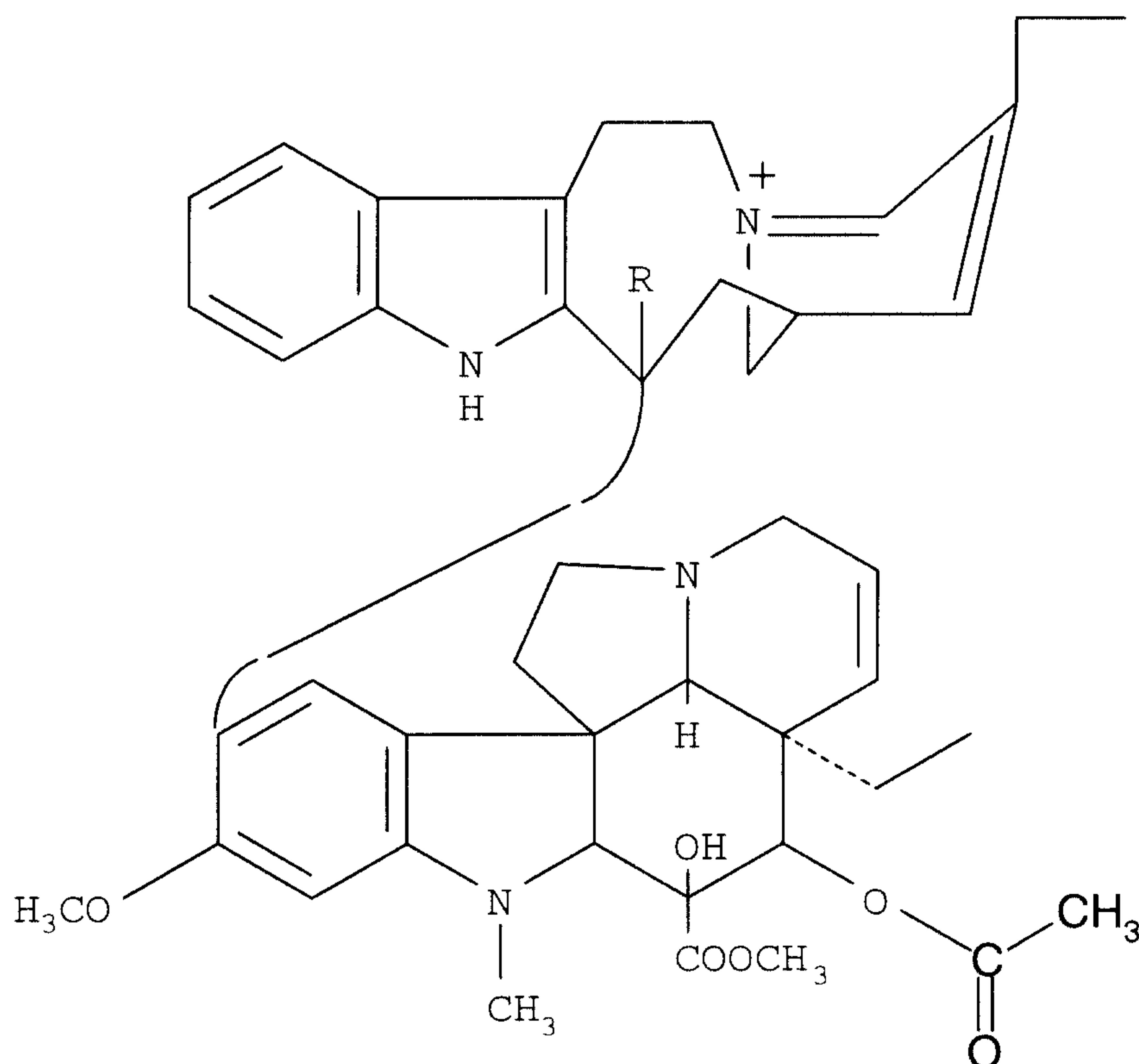
wherein R is the same as above, and without isolating said derivative;

- (b) treating said N-oxide derivative in the presence of at least one member selected from the group consisting of acetic anhydride, halogenated acetic anhydride, and acetyl chloride, to effect a Polonovski-type fragmentation reaction;

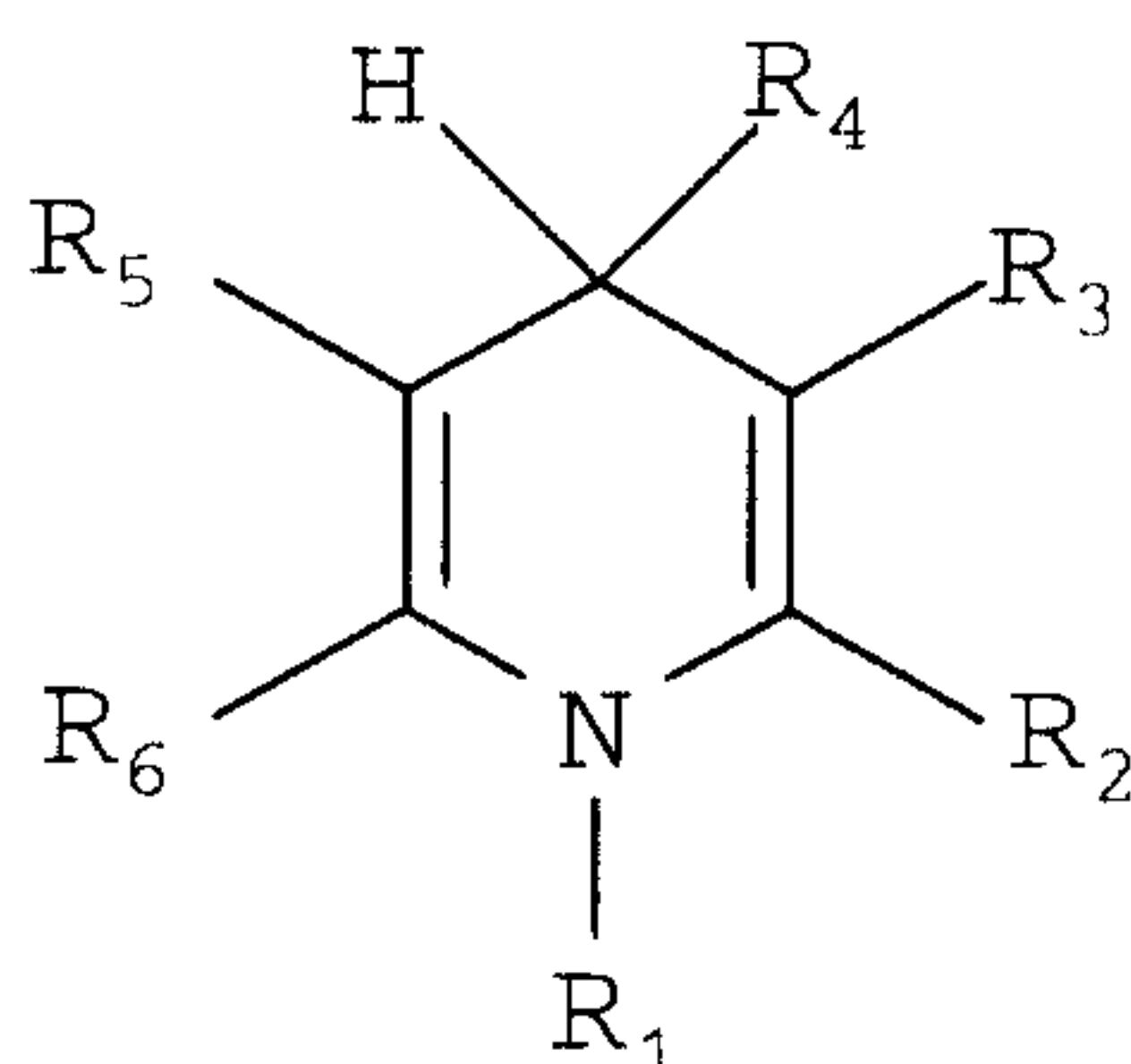
(c) without isolating the product of step (b), stereospecifically coupling said product of step (b) with a dihydroindole unit represented by the formula:



said coupling being conducted in the presence of at least one member selected from the group consisting of acetic anhydride, halogenated acetic anhydride, and acetyl chloride at a low temperature of about -70°C to about $+40^{\circ}\text{C}$, under inert conditions, to form a first iminium intermediate, represented by the formula:



(d) reducing said first iminium intermediate by reaction with a 1,4-dihydropyridine compound, represented by the formula:



wherein

R_1 is H, alkyl, substituted alkyl, aryl, substituted aryl and sugar units;

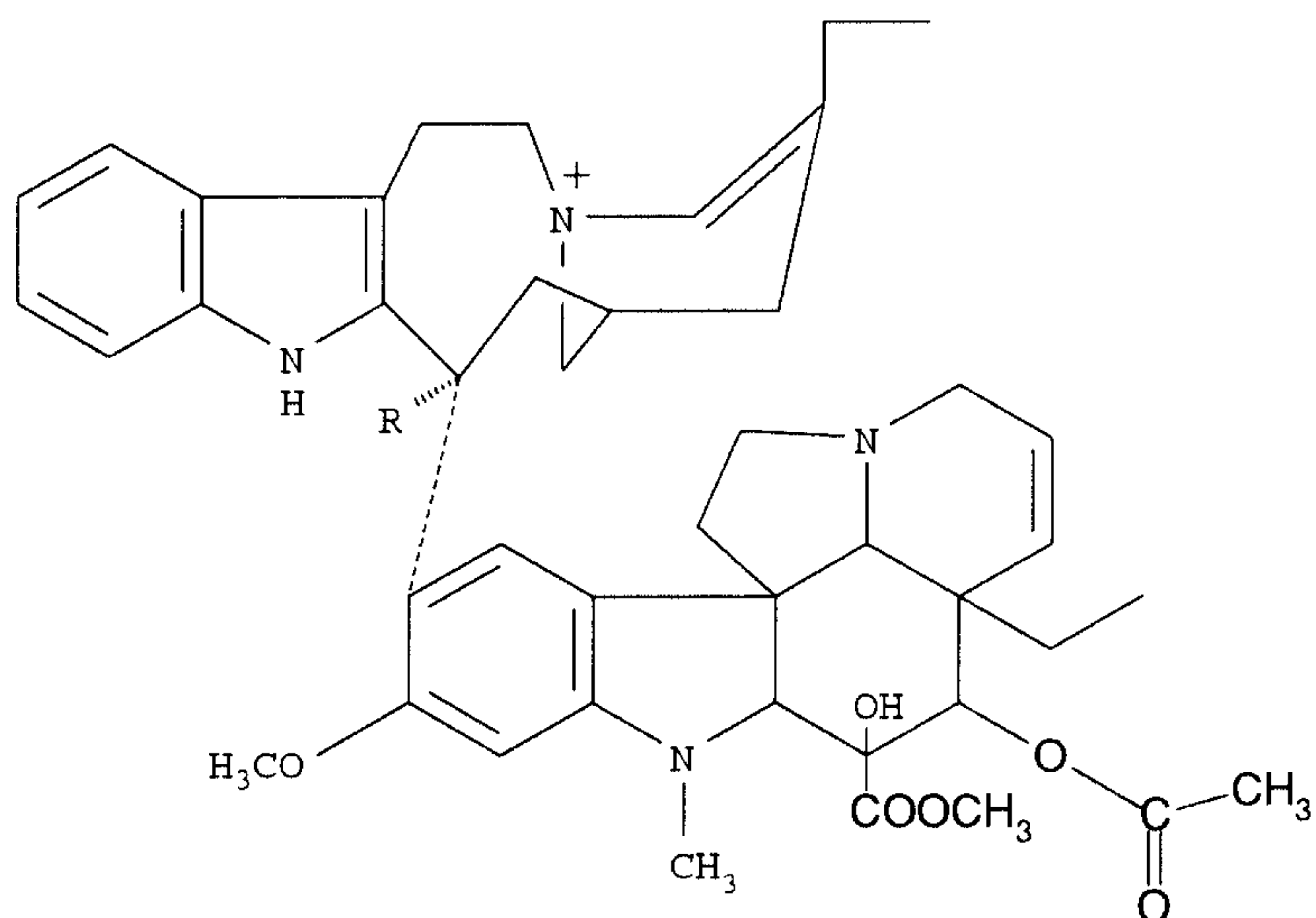
R_2 , R_4 and R_6 , independently, are H, alkyl or aryl;

R_3 is cyano, CONR_7R_8 wherein R_7 and R_8 independently may be H, alkyl, aryl, or taken together, R_7 and R_8 can form a ring structure containing up to four carbon atoms, said ring structure may further be substituted by $\text{CONR}_9\text{R}_{10}$, wherein R_9 and R_{10} are H or alkyl; and

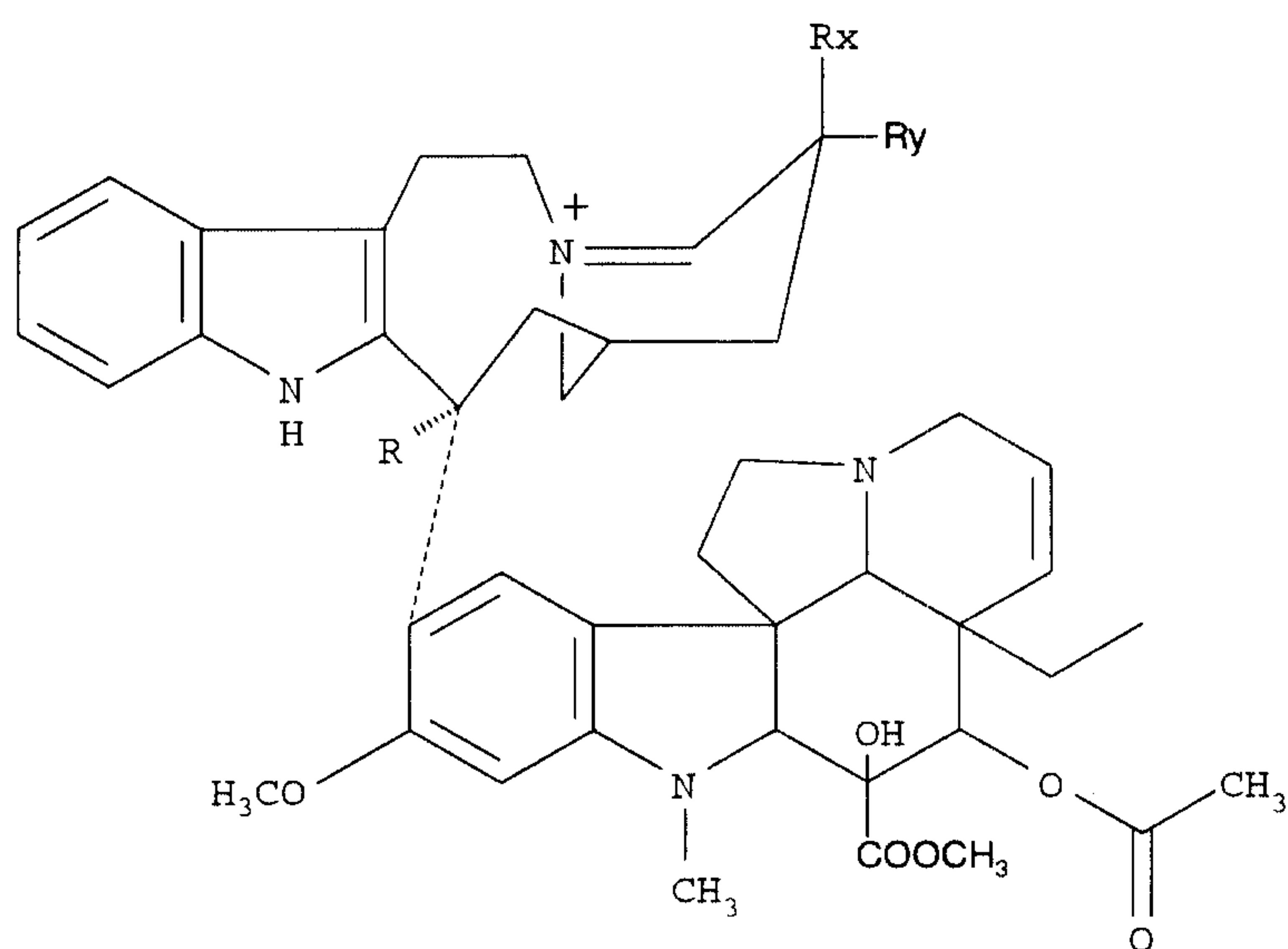
R_5 may be H, alkyl, carboxylate and salts thereof, and aryl;

with the proviso that, when R_3 is CONH_2 , and R_2 , R_4 , R_5 and R_6 are H, then R_1 is other than benzyl;

thereby forming an enamine intermediate, represented by the following formula:



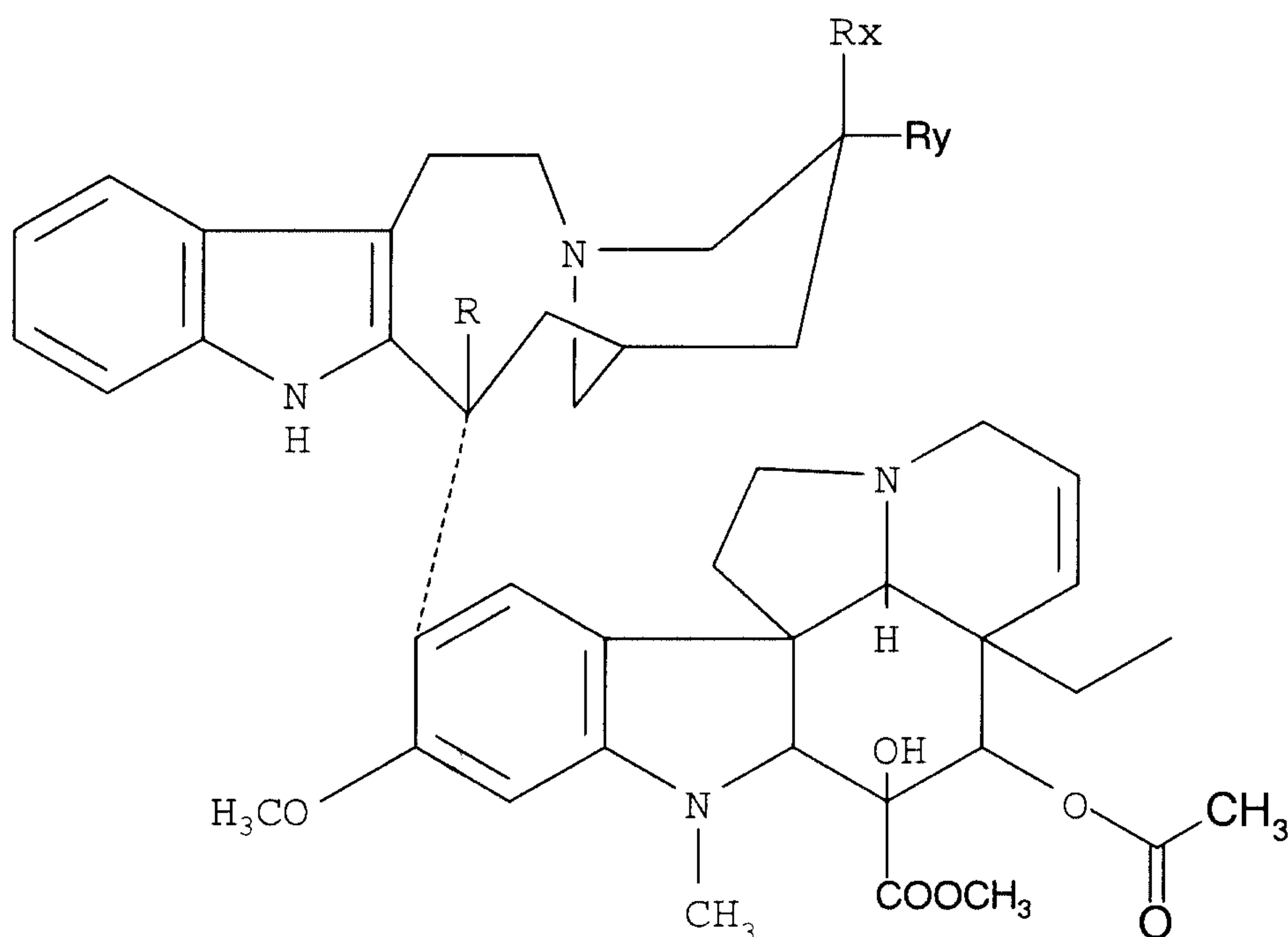
(e) transforming said enamine intermediates obtained in step (d) by oxidation under controlled aeration conditions in the presence of ferric chloride to a second iminium intermediate, as represented by the following formula:



wherein:

R_x is OOH or C_2H_5 and R_y is OOH or C_2H_5 , with the proviso that R_x and R_y cannot be the same; and

(f) reducing the second iminium intermediate obtained in step (e) to form said dimer alkaloid compounds, represented by the formula:



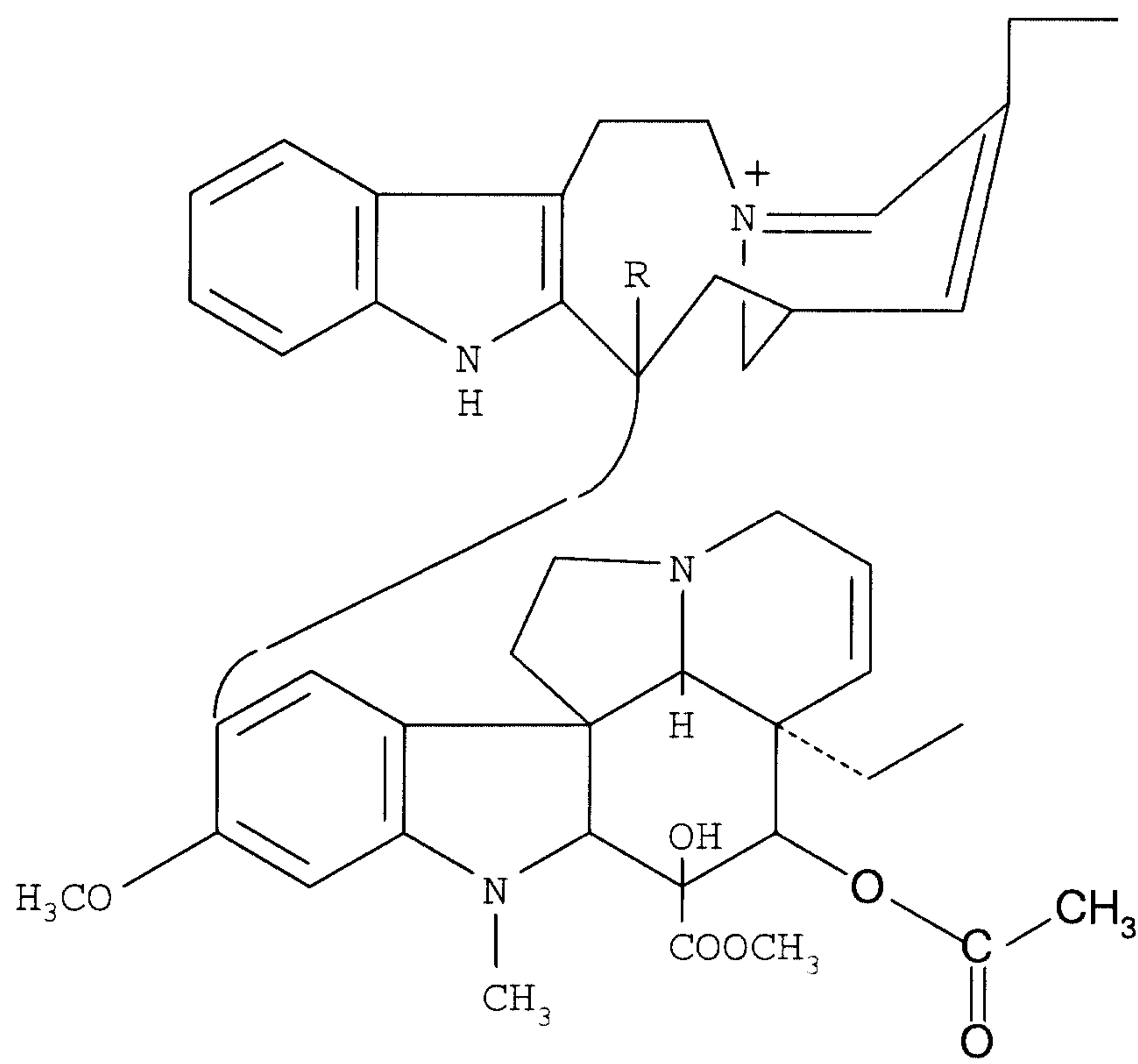
wherein: R_x and R_y are OH or C_2H_5 , with the proviso that R_x and R_y cannot be the same.

2. The process according to claim 1, wherein R1 is arylalkyl, diarylalkyl, alkoxy carbonylalkyl, dialkoxy carbonylalkyl, alkali metal salts thereof, and sugar units.
3. The process according to claim 1 or 2, wherein the 1,4-dihydropyridine reducing agent used in step (d) is selected from the group consisting of:
1-diphenylmethyl-(1,4-dihydronicotinamide);

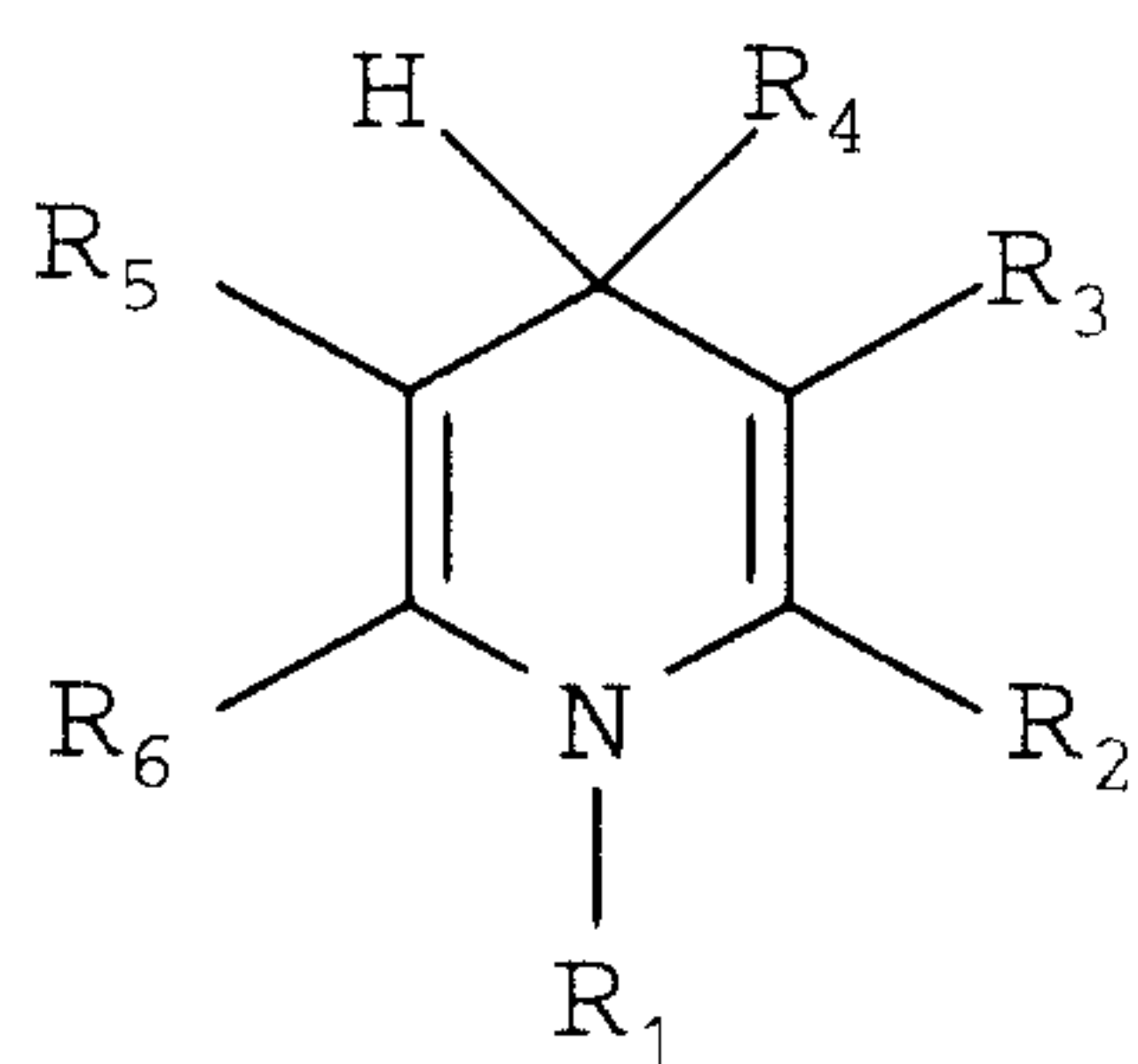
1-benzyl-3-cyano-1,4-dihydropyridine;
1-benzyl-1,4-dihydronicotinyl-(2'-carbamoyl-pyrrolidiny)-amide;
1,4-dihydro-1-(1-methoxycarbonyl isobutyl)-nicotinamide;
1-(2',3',4',6'-tetraacetyl-(beta)-D-glucopyranosidyl-1,4-dihydronicotinamide;
1,4-dihydro-1-(2'-methoxycarbonyl isopropyl)-nicotinamide;
1,4-dihydro-1-(1',2'-dimethoxy carbonyl ethyl)-nicotinamide; and
1,4-dihydro-1-(sodium-isobutyl-1-carboxylate)-nicotinamide.

4. The process according to anyone of claims 1 to 3, further including the step of diluting said enamine obtained in step (d) by a factor of 5 to 50 fold with a solvent prior to performing step (e).
5. The process according to anyone of claims 1 to 4, wherein the oxidative transformation step (e) is conducted at a pH in the range of 6-8.
6. The process according to anyone of claims 1 to 5, wherein about two equivalents of ferric chloride are employed in step (e).
7. The process according to anyone of claims 1 to 6, wherein the time of aeration in the oxidation transformation step (e) is from about five to about twenty minutes.
8. The process according to anyone of claims 1 to 7, wherein the oxidative transformation step (e) is conducted at a temperature in the range from about 0°C to about 20°C.
9. The process according to claim 4, wherein said enamine obtained in step (d) is diluted from about 5 to about 20 fold with a solvent, prior to performing step (e).
10. The process according to claim 9, wherein said enamine is diluted 8 to 12 fold.

11. A process according to anyone of claims 1-10, wherein R is COO-alkyl and alkyl group is C₁-C₃.
12. A process according to claim 11, wherein alkyl group is CH₃.
13. A process according to claim 12, wherein in the intermediate obtained in step (e), Rx is OH and Ry is CH₂CH₃ to obtain vinblastine and recovering said vinblastine.
14. A process according to claim 12, wherein in the intermediate obtained in step (e) Rx is CH₂CH₃ and Ry is OH to obtain leurosidine and recovering said leurosidine.
15. A process according to claim 12, further comprising the step of oxidizing said vinblastine to obtain vincristine, and isolating said vincristine.
16. A process for the production of 3',4'-anhydrovinblastine comprising the steps of:
 - (a) oxidizing catharanthine, said oxidation being carried out in the cold, at a temperature from about -77°C. to about +40°C, thereby oxidizing the bridge nitrogen of said catharanthine and forming an N-oxide derivative, and without isolating said derivative;
 - (b) treating said N-oxide derivative in the presence at least of one member selected from the group consisting of acetic anhydride, halogenated acetic anhydride, and acetyl chloride, to effect a Polonovski-type fragmentation reaction;
 - (c) without isolating the product of step (a), stereospecifically coupling said product of step (b) with vindoline said coupling being conducted in the presence of at least one member selected from the group consisting of acetic anhydride, halogenated acetic anhydride, and acetyl chloride at a low temperature of about -70°C to about +40°C, under inert conditions, to form a first iminium intermediate, represented by the formula:



- (d) reducing said first iminium intermediate by reaction with a 1,4-dihydropyridine compound, represented by the formula:



wherein

R_1 is H, alkyl, arylalkyl, diarylalkyl, alkoxy, alkoxycarbonylalkyl, dialkoxycarbonylalkyl, alkali metal salts thereof, carboxylate ester, aryl, and sugar units;

R_2 , R_4 and R_6 , independently, are H, alkyl or aryl;

R_3 is cyano, CONR_7R_8 wherein R_7 and R_8 independently may be H, alkyl, aryl, or taken together, R_7 and R_8 can form a ring structure containing up to four carbon atoms, said ring structure may further be substituted by $\text{CONR}_9\text{R}_{10}$, wherein R_9 and R_{10} are H or alkyl; and

R_5 may be H, alkyl, carboxylate and salts thereof, and aryl;
with the proviso that, when R_3 is CONH_2 , and R_2 , R_4 , R_5 and R_6 are H, then R_1 is other than benzyl.