RACEMISATION AND EPIMERISATION IN ISOQUINOLINE AND INDOLE ALKALOIDS

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Stereochemical changes at the chiral centres in isoquinoline and indole alkaloids and related compounds are reviewed.

I. Introduction

There are numerous examples of the epimerisation of an asymmetric centre, neighbouring a carbonyl group via loss of a proton by enolisation and reprotonation on basic or acidic treatment. It is very important for the synthesis of natural products that the desired configuration is set up by epimerisation, however the equilibration of a compound with only one chiral centre leads inevitably to racemisation. Racemisation is also important, particularly from the industrial point of view, if the unwanted antipode which remains after resolution can be converted into the desired antipode. We would now like to review the stereochemical changes that take place at the chiral centre in isoquinoline and indole alkaloids and related compounds.

II. Epimerisation in Indole Alkaloids

Inversion at the C-3 position of a tetrahydrocarboline by treatment with acid is mechanistically feasible and also well documented.[1-4]

This disposition was ingeniously utilized for the total synthesis of reserpine (5) by Woodward.[1] The quaternary salt (1) was reduced by sodium borohydride to the tetrahydrocarboline (2) since the hydride approached from the less hindered side. However, although more stable, compound (2) had the wrong configuration at C-3 position for reserpine.

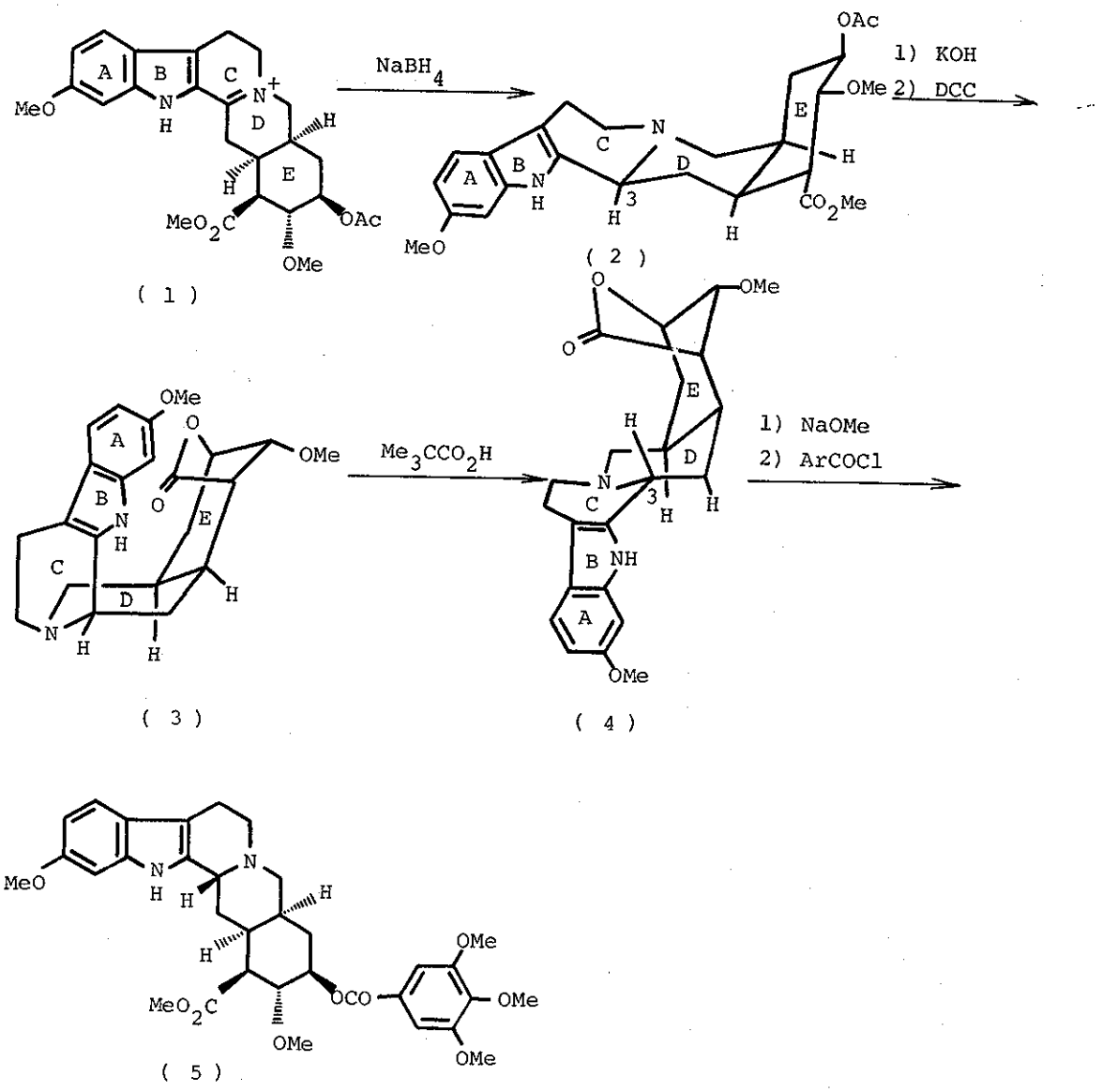
Therefore, both ester groups of 2 were hydrolysed and then lactonised with dicyclohexylcarbodiimide to yield 3. Since the substituents in ring E were now necessarily axial, the normally flexible cis-decalin type of system in ring D and E was rigidly fixed with the result that, if chair conformations were to be maintained, the indole ring joined to ring C must be axial. However, if inversion at the C-3 position would occur, the indole ring would be equatorial. This was accomplished by heating with pivalic acid where 3 isomerised at the C-3 position to give the lactone (4). Methoxide in methanol opened the lactone and acylation with 3,4,5-trimethoxybenzoyl chloride then gave (±)-reserpine (5).

Chart 1

Examples of base promoted epimerisation at the C-3 position of tetrahydrocarbolines have been reported[3,5], though the conditions required were vigorous and consequently poor yields were obtained. On the other hand, the ease of epimerisation with acid depends upon steric as well as electronic factors associated with the substitution of the benzene ring.[4]

Three mechanism could be considered to account for the acid catalyzed epimerisation of tetrahydrocarbolines.[6] The three posibilities,

Chart 1

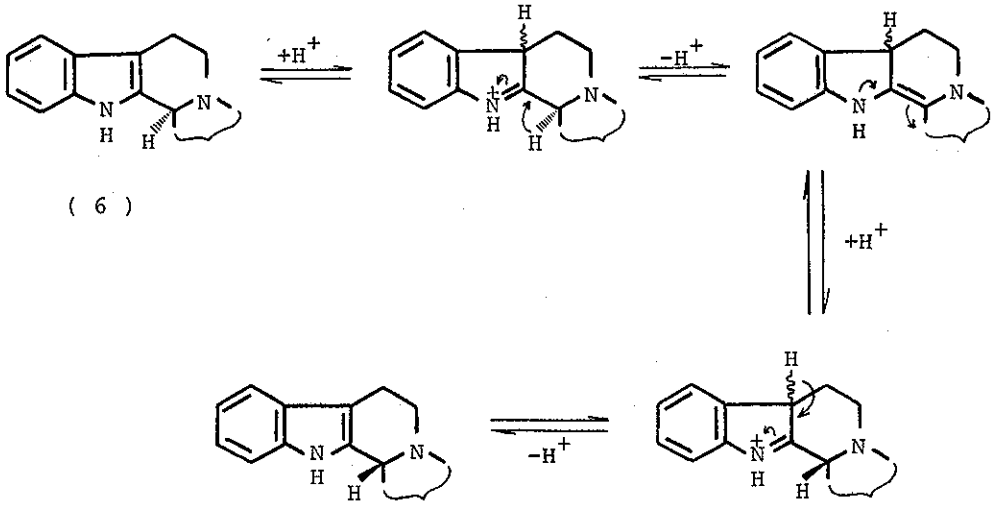

NaBH4
1) KOH
2) DCC
Me3CCO2H
1) NaOMe
2) ArCOCl
MeO
MeO2C
OAc
OMe
CO2Me
NH
(1)
(2)
(3)
(4)
(5)

involving initial protonation at one of three atoms, are represented in Charts 2,3 and 4.

Chart 2, 3, 4

In Chart 2, a proton is first added to the indole β-position at C-7. A series of enamine-immonium equilibra, proceeding through a trigonal intermediate at the C-3 position, would then allow to epimerise to 7. Chart 3 involves the expulsion of a protonated N^4, followed by re-addition while Chart 4 represents the initial attack by a proton occurring at the C-2 position of the indole α-position leading to a ring-opened intermediate possessing a planar C_3 atom which would thus permit a reclosure of the system to both epimers. However, since heating 3-deuterio-isoreserpine (10)[7], prepared by sodium borodeuteride reduction of 3-dehydroreserpine perchlorate, with acetic acid gave a mixture of the epimers (8 and 10) without loss of the label, the mechanism shown in Chart 2 can be excluded. Alternatively, since reserpine and isoreserpine methosalts do not epimerise at the C-3 position in acetic acid, this favors the initial protonation at C-2 position according to Chart 4. Finally, since deserpidine (9) epimerises much more slowly than reserpine but eventually yields an equilibrium mixture of analogous composition, the faster rate in the reserpine series is consistent with the mechanism involving initial protonation at the C-2 position.[6]

Chart 2



(6)

(7)

Chart 3

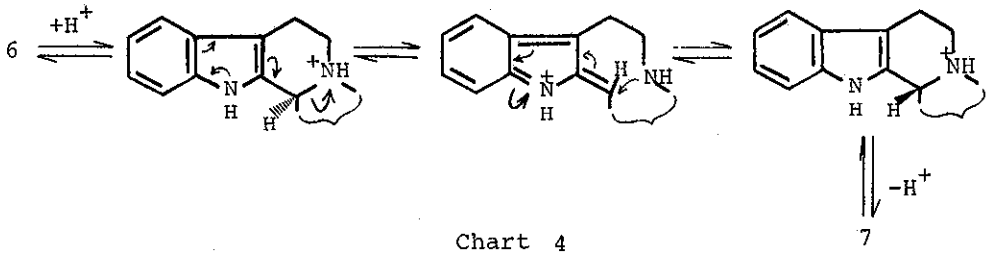


Chart 4

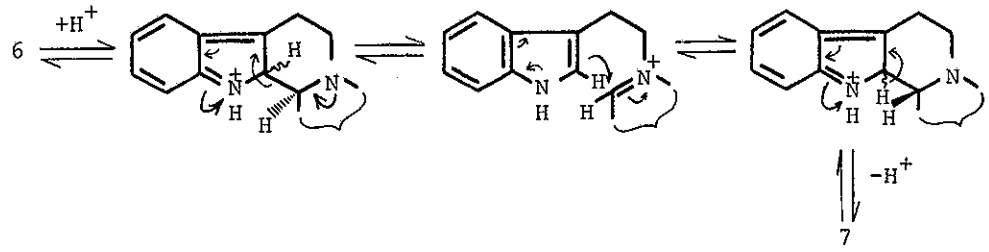
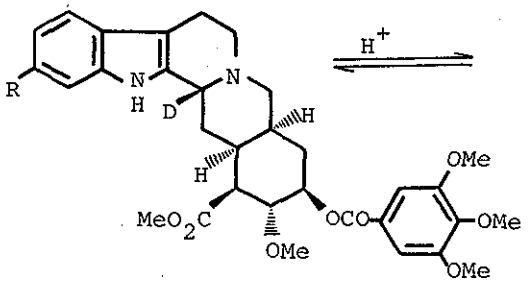
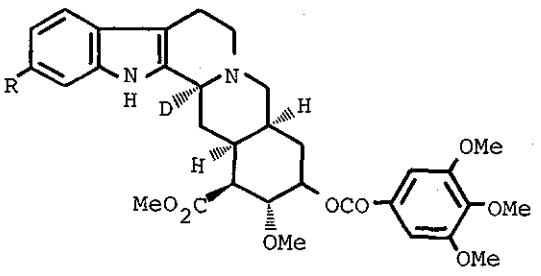


Chart 5



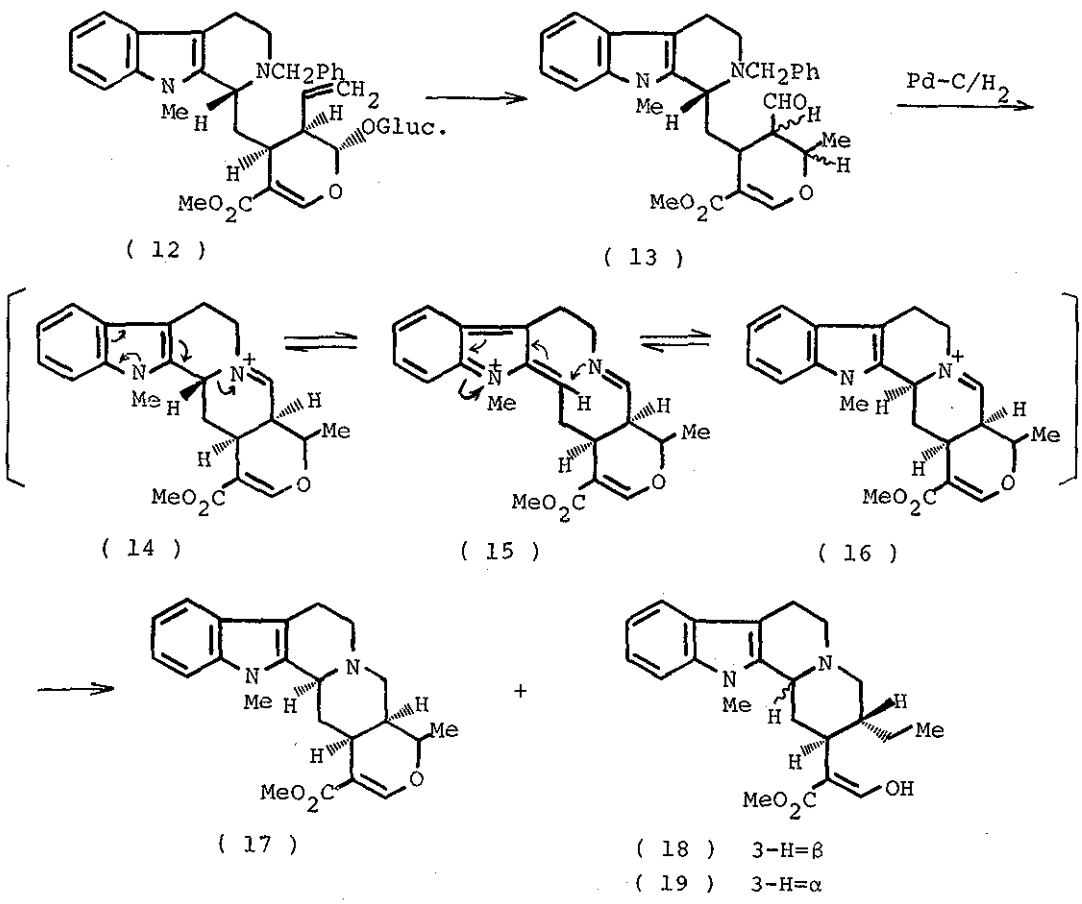
(8) R=OMe
(9) R=H



(10) R=OMe
(11) R=H

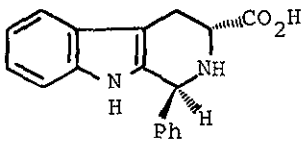
Removal of the sugar from N^4-benzyl-N^1-methylvincoside (12) gave two major products (13), isomeric with a simple aglycone, which on hydrogenation with palladium - charcoal in methanol and acetic acid gave three compounds. The major components were methyltetrahydroalstonine (17) and 3β , 20β -N^1-methyldihydrogeissoschizine (18). The minor component was the 3α -isomer (19) of 18.[8] It is known from previous experiments[9] that the hydrogenation using palladium-charcoal does not cause inversion at the C-3 position. Deuteriation studies confirmed that the hydrogen at the C-3 position was retained throughout. It is therefore postulated that isomerisation occurs by the cleavage between the C-3 and N-4 bonds in the obligatory immonium intermediate (14) followed by recyclisation.[8] The mechanism is simlar to that shown in Chart 3.

Chart 6



Although the mechanism shown in Chart 2 was not involved in the epimerisation of the above examples, it is, however, interesting that 1,2,3,4-tetrahydro-3-phenylcarboline-5-carboxylic acid (20) was incorporated with deuterium at the C-1 position, when epimerisation was carried out with deuterium chloride in deuteriomethanol. This suggests the participation of the mechanism as in Chart 2.[10]

Chart 7



(20)

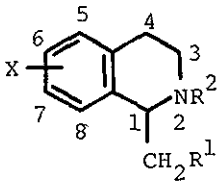
III. Racemisation and Epimerisation in Isoquinoline Alkaloids

The chiral centre at the C-1 position of non phenolic tetrahydroisoquinolines is not effected by the usual acidic or basic reagents. Special conditions are required for a steric change at the chiral centre at the C-1 position.

1. Heating at an Elevated Temperature

Hydrochlorides of optically active tetrahydroisoquinolines (21a-f) having at least one hydroxyl group at C-6 or 7 position were racemised by heating. Namely, the hydrochloride of (+)-21d was heated for 30 min at 180 - 185° in vacuo to give the hydrochloride of the racemate in 76.5 % yield. The racemisation of the 6-hydroxyl bases (21a-d) is easier than that of the 7-hydroxyl ones (21e and f). Even though free base, the formers (21a-d) were racemised at the elevated temperature. Ring-opened intermediate (23) was postulated for the racemisation of the 6-hydroxyl compounds.[11a]

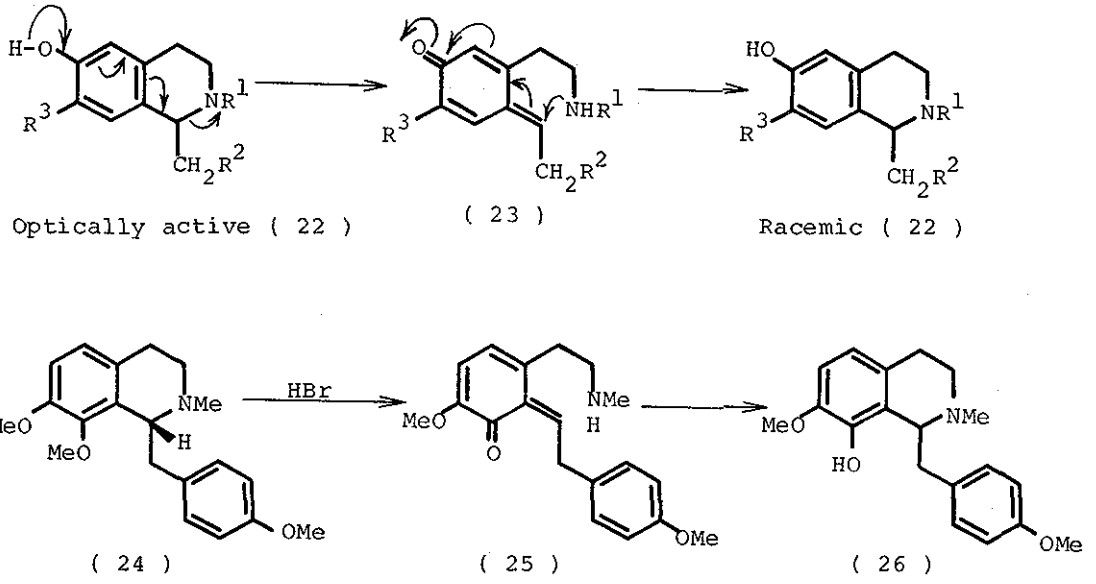
Chart 8



(21)

	R^1	R^2	X
a	Phenyl	H	6-OH
b	Cyclohexyl	H	6-OH
c	Phenyl	Me	6,7-$(OH)_2$
d	3,4,5-Trimethoxyphenyl	H	6,7-$(OH)_2$
e	Phenyl	H	7-OH
f	Cyclohexyl	H	7-OH

Chart 8 (continued)



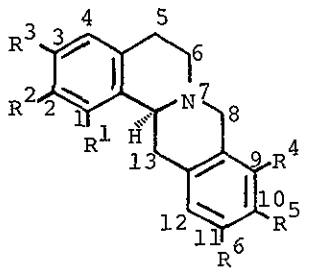
Brossi also found that heating optically active O-methylnorpetaline (24) with concentrated hydrobromic acid gave racemic norpetaline (26) and proposed an ionic mechanism involving a ring-opened intermediate (25).[11b]

2. Catalytic Hydrogenation

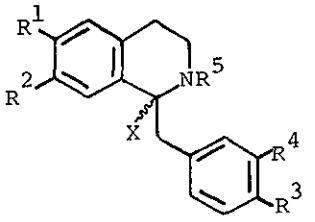
Protoberberines[11,12] and 1-benzyltetrahydroisoquinolines[13,14,15] were racemised at room temperature by stirring with Adams catalyst under hydrogen atmosphere. Reaction conditions for the racemisation

of alkaloids and related compounds (Chart 9) are given in Table 1.

Chart 9



(27) $R^1=R^6=H$, $R^2=R^3=R^4=R^5=OMe$
(28) $R^1=R^4=H$, $R^2=R^3=R^5=R^6=OMe$
(29) $R^1=R^2=R^3=R^4=R^5=OMe$, $R^6=H$
(30) $R^1=R^4=H$, $R^2=R^6=OH$, $R^3=R^5=OMe$
(31) $R^1=OH$, $R^2=R^3=R^4=R^5=OMe$, $R^6=H$



(32) $R^1=R^2=R^3=R^4=OMe$, $R^5=Me$, X=αH
(33) $R^1=R^2=R^3=R^4=OMe$, $R^5=H$, X=αH
(34) $R^1=OMe$, $R^2=OCH_2Ph$, $R^3=OH$, $R^4=H$, $R^5=Me$, X=αH
(35) $R^1=OMe$, $R^2=R^3=OH$, $R^4=H$, $R^5=Me$, X=βH
(35a) $R^1=R^3=OMe$, $R^2=R^4=OH$, $R^5=Me$, X=αH

All of the alkaloids-types shown in Table 1 were racemised with Adams catalyst in protic solvents. While racemisation of non-phenolic bases (27, 28, 29, 32, and 33) required reaction times of 30 ∿ 50 hr, phenolic bases required longer reaction times: 96 ∿ 112 hr for the monophenolic bases (31 and 34) and 129 ∿ 165 hr for the diphenolic

Table 1

Racemisation of Tetrahydroprotoberberines and 1-Benzyltetrahydroisoquinolines with Adams Catalyst

Compound	Reaction Time (hr)	Solvent
27	42	AcOH
28	36	AcOH
28	42	EtOH
29	50	MeOH
30	165	AcOH
31	96	MeOH
32	45	AcOH
32	45	EtOH
33	48	AcOH
33	48	EtOH
34	112	EtOH
35	129	EtOH

bases (30 and 35). However, (-)-1,2,3,4-tetrahydro-6,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)isoquinoline (26), because of its catechol function, could not be racemised. Finally, the hydrochlorides of the above bases could not be racemised under the same conditions as above,[12,13,14] although Merck group reported that optically active reticuline hydrochloride was completely racemised on hydrogenation over platinum in ethanol for 24 hr.[15]

In order to study the mechanism of racemisation, S-[13,13,13a-D_3]-xylopinine (40) and S-[13,13,13a-D_3]coreximine (42) were synthesised as follows. The 3,4-dihydroisoquinolines (36 and 37) were reduced with zinc powder and deuterioacetic acid[16] to the trideuterioisoquinolines (38 and 39). The racemate of [1, $\alpha\alpha$-D_3]-1,2,3,4-tetrahydropapaverine (38) was resolved with (-)-N-acetylleucine to give the S-isomer, which was heated with formalin in the presence of hydrochloric acid to give 40. Mannich reaction of 39 yielded the racemate of [13,13,13a-D_3]-O,O-dibenzyloxycoreximine, the resolution of which with (+)-di-p-toluoyltartaric acid, followed by debenzylation of the resulting 41 with ethanolic hydrochloric acid, afforded 42.

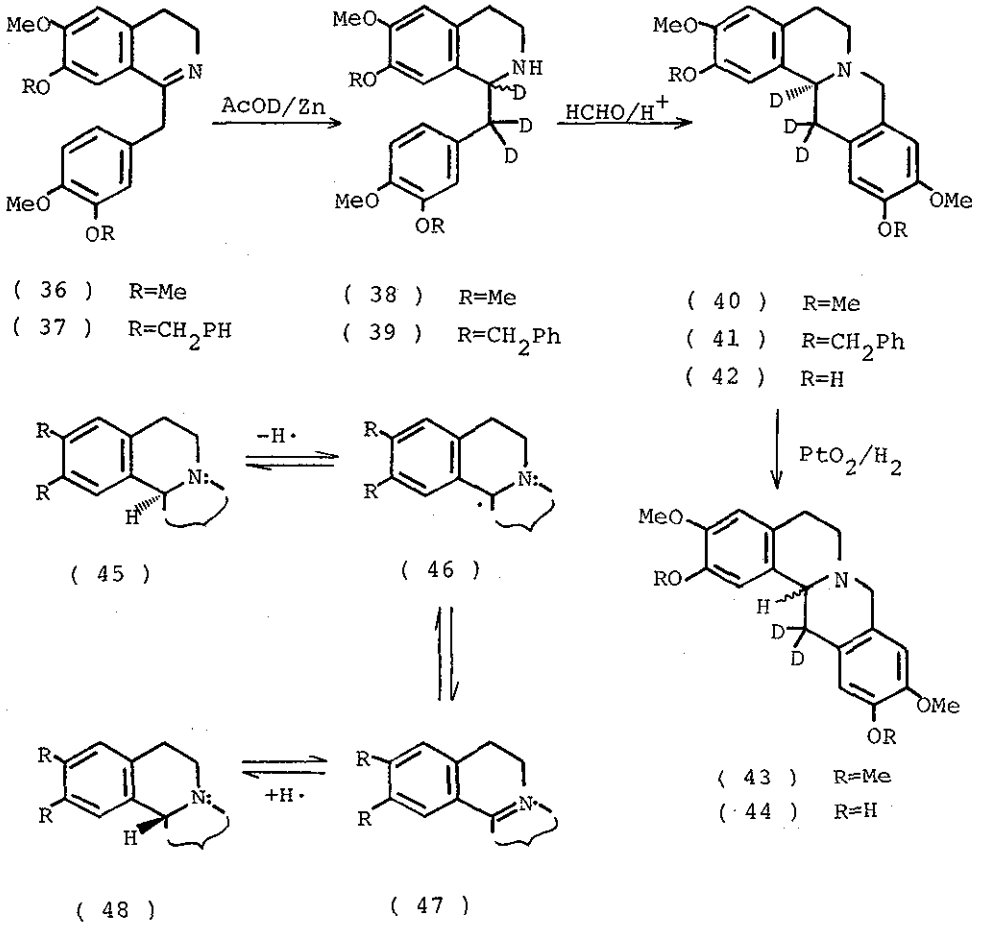
When both trideuterioprotoberberines (40 and 42) were treated with Adams catalyst under hydrogen atmosphere, racemisation occurred with replacement of the deuterium at the C-13a position with hydrogen. This was determined by comparison of the mass spectra of the racemised products with those of the starting trideuterioprotoberberines.[12]

However, in the case of catalytic hydrogenation of (-)-[13,13,13a-D_3]xylopinine (40) with either palladium oxide, palladium charcoal, or W_2 - Raney nickel in several solvents, no racemisation was observed nor was deuterium exchanged with hydrogen.

It is thus considered that alkaloid-types (45) are absorbed on Adams catalyst and then the C_{13a}-H bond is ruptured homolytically to afford the radical (46), which is equilibrated to a trigonal intermediate (47). Phenolic substituent would slow down the hydrogen abstraction. On the other hand, palladium and nickel catalysts seem to have less affinity than platinum for the alkaloids. Recently this recemisation

over platinum catalyst was applied for that of optically active aporphines.[17]

Chart 10



(36) R=Me
(37) R=CH_2PH

(38) R=Me
(39) R=CH_2Ph

(40) R=Me
(41) R=CH_2Ph
(42) R=H

(43) R=Me
(44) R=H

(45) (46) (47) (48)

When the above reaction using Adams catalyst was applied to isoquinoline alkaloids having another chiral centre, epimerisation occurred. Catalytic hydrogenation of (±)-kreysiginone (52, X=H) and its epimer (53, X=H) in the presence of platinum catalyst gave

the same mixture of the two racemic cyclohexanols (54).

In contrast, reduction of the hydrochlorides of both epimers (52 and 53) on palladium-charcoal provided the products reduced at the *carbon-carbon* double bonds without epimerisation at the C-6a position.

Similar treatment of the racemic deuteriated dienones (52 and 53, X=D), prepared by reduction of the methiodide (49) with sodium borodeuteride followed by debenzylation of the monophenol (50) and phenol oxidation of the resulting phenol (51) with *ferric chloride*, in the presence of platinum oxide furnished a mixture of 54.[18]

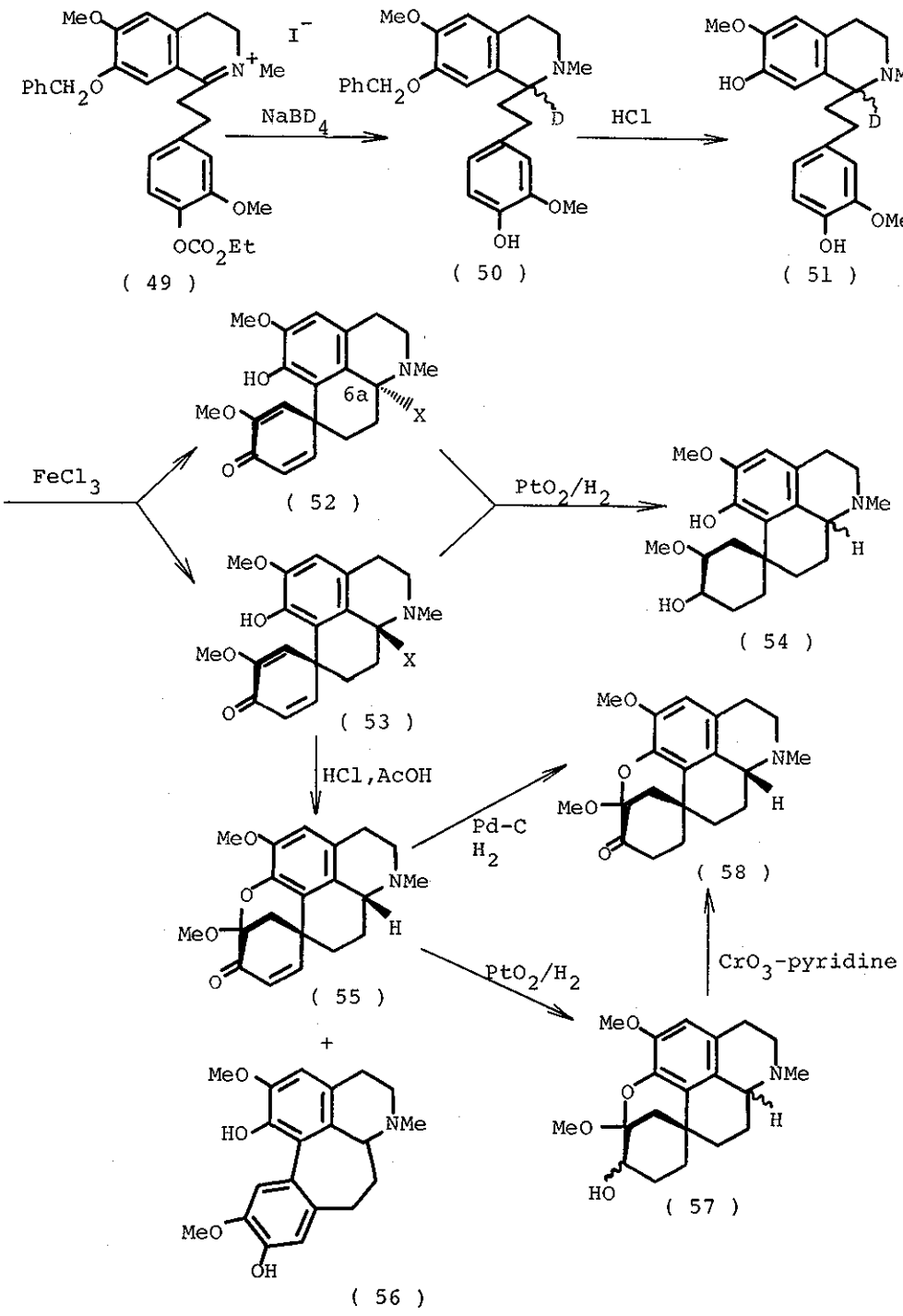
Treatment of the (±)-kreysiginone epimer (53) with concentrated hydrochloric acid in glacial acetic acid yielded homoproaporphine (55) together with the dienone-phenol rearrangement product, homoaporphine (56). The homoproaporphine (55) was subjected to the hydrogenation in the presence of Adams catalyst to afford a mixture of two cyclohexanols (57), which were epimeric at the C-6a position to each other. On the other hand, reduction of 55 on palladium-charcoal provided the cyclohexanone (58), which was also obtained from one of the above cyclohexanols (57) by oxidation with chromic anhydride-pyridine complex in methylene chloride,[19] indicating no epimerisation at the C-6a position with palladium catalyst.

Chart 11

3. Photolytic Reaction

Ninomiya and his co-workers reported isomerisation during photocyclisation of certain enamides. Irradiation of some B/C-

Chart 11


MeO
PhCH2O
I−
N+Me
NaBD4
NMe
D
HCl
HO
OMe
OCO2Et
OH
(49)
(50)
(51)
6a
X
FeCl3
PtO2/H2
(52)
(53)
(54)
HCl,AcOH
Pd-C
H2
(55)
(56)
(57)
(58)
CrO3-pyridine

trans-benzo[c]phenanthridinones which were substituted with an electron-withdrawing group such as ester and nitrile effected isomerisation to the corresponding cis-lactams.

Irradiation of a methanolic solution of the enamide (58, X=CO_2Me) with a low pressure mercury lamp for 7 hr yielded sterospecifically, according to the electrocyclic mechanism, the trans-lactam (59, X=CO_2Me). However, prolonged irradiation of 58 (X=CO_2Me) for 20 hr gave the cis-lactam (60, X=CO_2Me) as the sole product in 20 % yield. Further, the trans-lactam (59, X=CO_2Me) was quantitatively isomerised to the cis-lactam (60, X=CO_2Me) when irradiated in methanol. However, this isomerisation was not observed when an aprotic solvent such as benzene, ether or dioxane was employed.

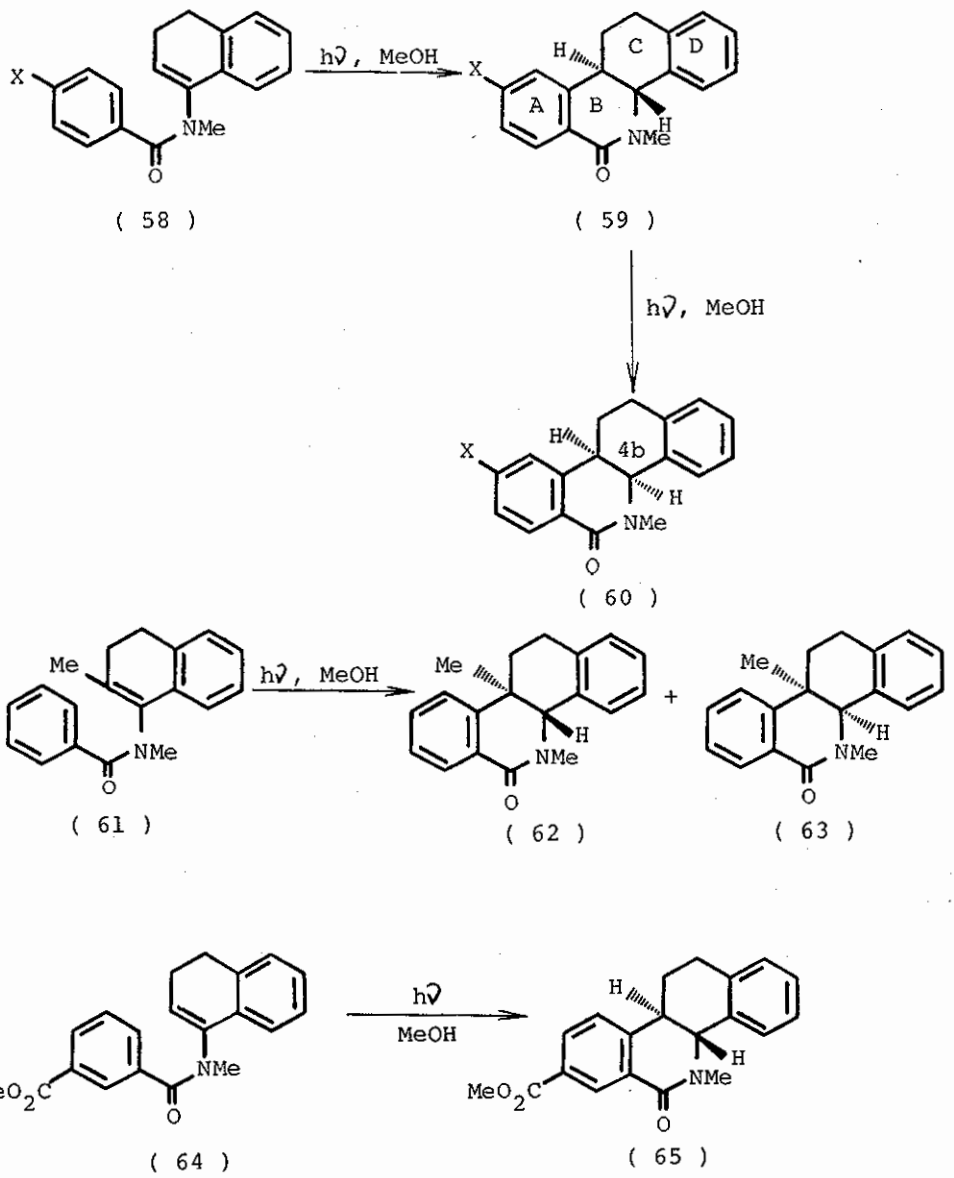
Photocyclisaiton of the enamide (58, X=CN) having a cyano group at the para position afforded the same result, while the p-methoxy-substituted enamide (58, X=OMe) gave only the trans-lactam. Irradiation of the enamide (58, X=H) for several hours afforded the trans-lactam (59, X=H), while a prolonged irradiation of 59 (X=H) for 10 days brought about isomerisation to provide cis-lactam (60, X=H) in 10 % yield.[20]

Irradiation of the enamide (61) for 40 hr gave the trans (62) and cis-lactams (63) in 1 % and 7 % yield, respectively.[21] On the other hand, irradiation of the enamide (64) carrying an ester group at the meta position gave the trans-lactam (65) which decomposed upon a prolonged irradiation.

Furthermore, irradiation of the enamide (58, X=CO_2Me) in deuterium methoxide solution furnished a mixture of two isomers, ——— the trans-lactam was devoid of deuterium whereas the cis-lactam contained

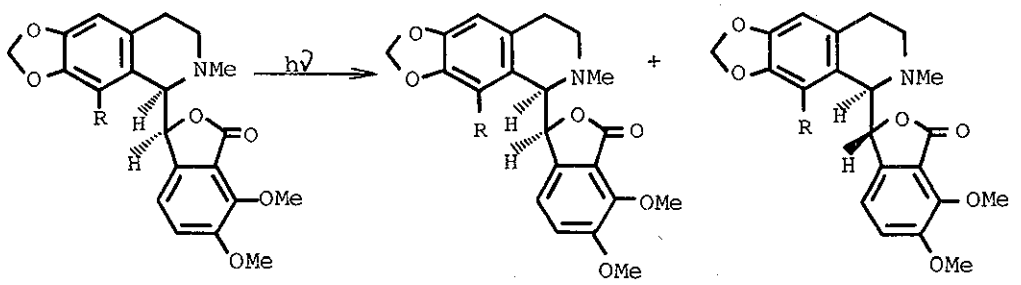
one deuterium at the C-4b position. The mechanism of this isomerisation is still unclear.[20]

Chart 12



Recently, it was found that photolysis of optically active phthalideisoquinoline brought about stereochemical changes at the two chiral centres to afford a racemic mixture of epimers. Thus irradiation of (-)-α-narcotine (66) in dry tetrahydrofuran with a high pressure mercury lamp equipped with a pyrex filter gave (±)-α-narcotine (68) and (±)-β-narcotine (70). Similarly, photolysis of (-)-β-hydrastine (67) afforded (±)-α-hydrastine (69) and (±)-β-hydrastine (71). The mechanism of racemisation is still obscure.[22]

Chart 13



l-form

(66) R=OMe

(67) R=H

dl-form

(68) R=OMe

(69) R=H

dl-form

(70) R=OMe

(71) R=H

IV. Conclusion

It is well known that stereoisomers, even through enatiomeric, show sometimes completely different biological activities. Therefore, optical resolution of synthetic compound can become quite important and racemisation becomes consequently important for utilisaiton of the unwanted antipode. Hopefully, in the near future,

newer methods for the racemisation and epimerisation of rather inert compounds will be developed.

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Received, 23rd June, 1976