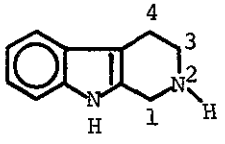
The Spiroindolenine Intermediate, A Review

Frank Ungemach and James M. Cook,* Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201

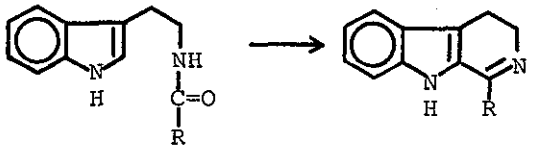
The Pictet-Spengler reaction has been employed to prepare 1,2,3,4-tetrahydro-β-carbolines for many years and is presumed to go through the spiroindolenine intermediate (XIX). A review of the evidence for this mechanism is presented.

Tetrahydro-β-carbolines (I) have been synthesized principally

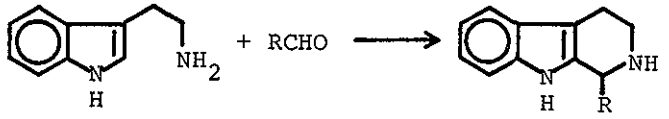


I

by the Bischler-Napieralski reaction (1) (Eq 1) and the Pictet-Spengler condensation (2-5) (Eq 2). Other methods (2-6) have



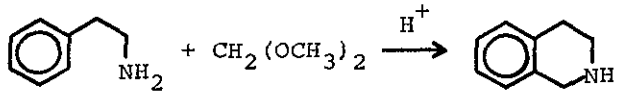
(1)



(2)

also been employed such as the Fischer indole cyclization; however, the Pictet-Spengler reaction is the topic of pincipal interest here and will be described in some detail.

Pictet and Spengler (7) conceived the idea for the method based on biogenetic grounds, for it was felt that isoquinoline alkaloids were formed in plants by the condensation of β-arylethyl-amines with carbonyl compounds; the condensation of β-phenethyl-amine (II) with methylal (Eq 3) in hydrochloric acid (conc)

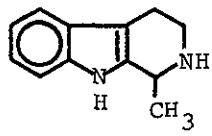


(3)

II III

resulted in the formation of 1,2,3,4-tetrahydroisoquinoline (III). The Pictet-Spengler reaction soon became a standard method for the formation of tetrahydroisoquinolines (2,8).

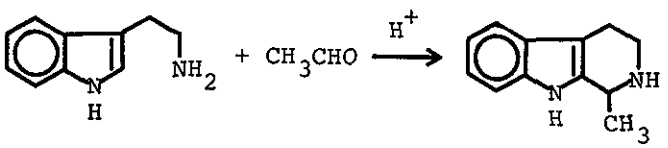
Apparently, Tatsui (9) was the first to utilize this method with indole bases, specifically, the synthesis of 1-methyl-1,2,3,4-tetrahydro-β-carboline (tetrahydroharman IV). A number of reviews



IV

(2-6) are available which list the numerous β-carboline syntheses which follow Tatsui's original adaptation of the Pictet-Spengler condensation. A selected set of examples will be presented here to illustrate the scope of this reaction.

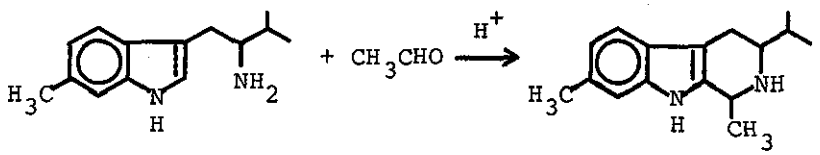
Many syntheses have been modeled after the synthesis of tetrahydroharman (IV) as reported by Akabori and Saito (10). Tryptamine and acetaldehyde were condensed in a 0.3 N sulfuric acid solution, which was heated to 110°C for 20 minutes to facilitate condensation (Eq 4). In 1971, the amine (V) was heated



(4)

IV

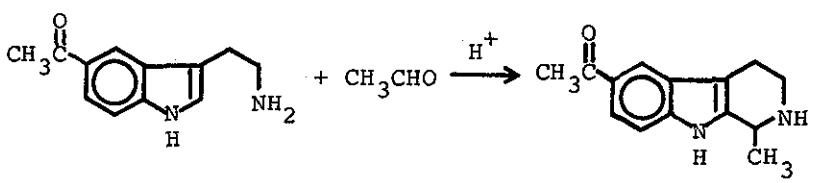
with acetaldehyde in a 0.4 N sulfuric acid solution for one hour to produce the substituted tetrahydro-β-carboline (VI) (Eq 5) (11).



(5)

V VI

Similarly, the acetyl carboline derivative (12) (VII) was formed from the reaction of acetaldehyde and 5-acetyltryptamine (VIII) in 1 N sulfuric acid (Eq 6). Similar results have been reported



(6)

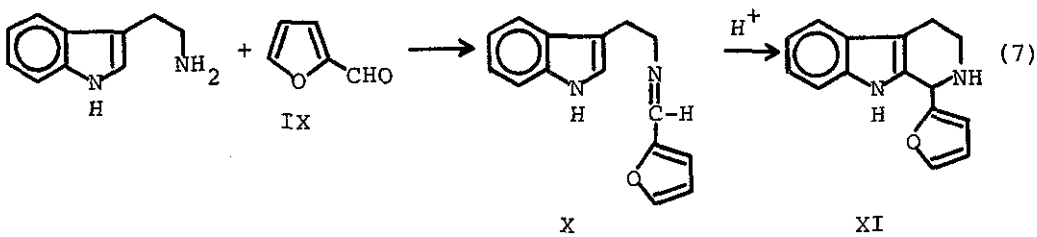
VIII VII

using other aldehydes (13). In addition to tryptamine, tryptophan (2-6,14,15) has been condensed with a whole host of aldehydes,

from formaldehyde to substituted benzaldehydes (2-6,12,13).

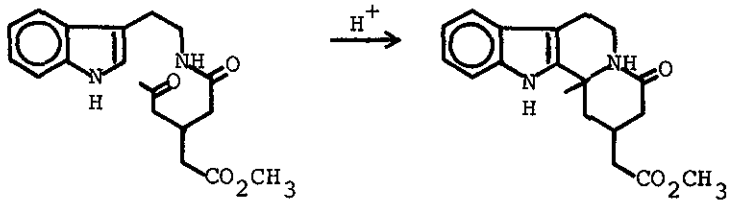
Sulfuric acid (2-6,11-13), hydrochloric acid (2-6,12,13,16), and acetic acid (17) have been used as catalysts. The experimental conditions fall into two general categories (2). Laboratory conditions which employ a 20-30% excess of acid, accompanied by heating, while physiological conditions require buffers to maintain the pH between 3 and 8. When the pH is 7 or higher, air oxidation becomes the predominate factor and yields tend to suffer (18).

One recent alteration of this reaction has been carried out by initial formation of the Schiff base in an aprotic solvent followed by formation of the β-carboline in acidic media (12,19-21). For example, a mixture of tryptamine and furfural (IX) were refluxed in benzene to form the Schiff base (X); a Dean-Stark trap was used to remove the water formed in the reaction. The Schiff base (X) was transformed to the tetrahydro-β-carboline (XI) by treatment with anhydrous HCl in tetrahydrofuran (Eq 7) (19).



(7)

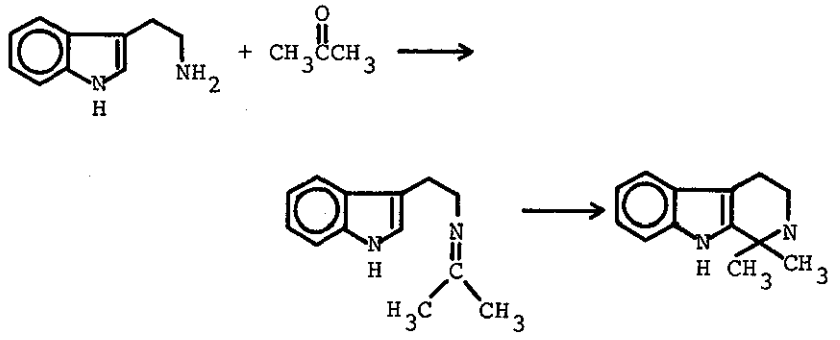
In addition to aldehydes, other carbonyl compounds have been employed; reactions with lactones, however, are rare. The keto-amide (XII) has been reported by Winterfeldt (22) to cyclize in methanolic hydrogen chloride to the tetracyclic lactam (XIII) (Eq 8). Acetone and tryptamine were condensed in benzene, in the



(8)

XII XIII

presence of p-toluenesulfonic acid, by Hester (23) to provide the Schiff base (XIV). The Schiff base (XIV) was then cyclized in phosphorous oxychloride to furnish 1,1-disubstituted tetrahydro-β-carboline (XV) (Eq 9). An interesting report appeared in 1973 (24)

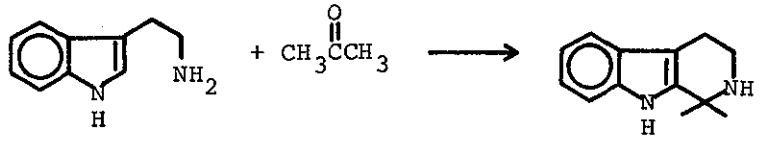


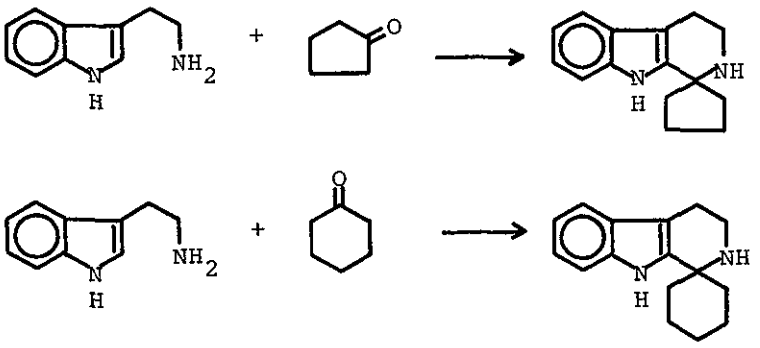
(9)

XIV XV

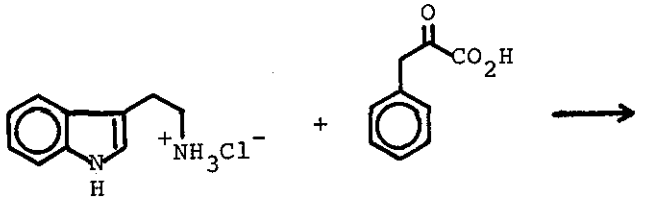
which described a method for the condensation of tryptamine with various ketones in the presence of ethyl polyphosphate (Scheme 1).

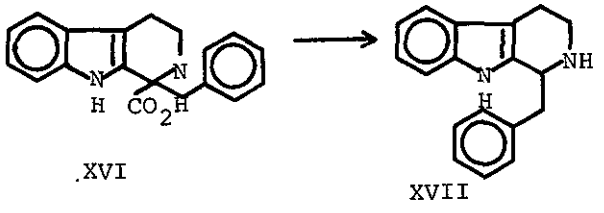
SCHEME 1



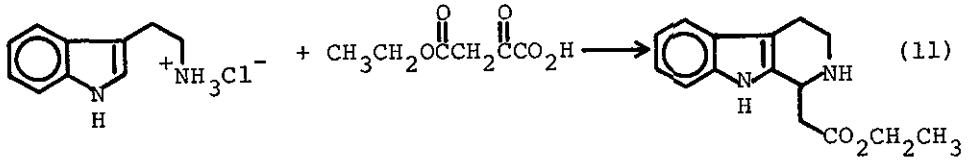


α-Keto acids and tryptamine hydrochloride have been condensed in protic solvents to form 1-carboxy-tetrahydro-β-carbolines (XVI). These acids undergo facile decarboxylation to yield the tetrahydro-β-carboline (XVII) (Eq 10) (21); an example is shown in Eq 11 (25).



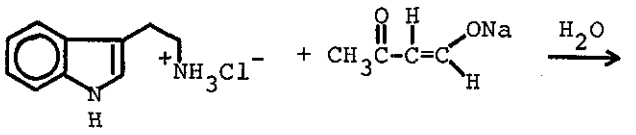


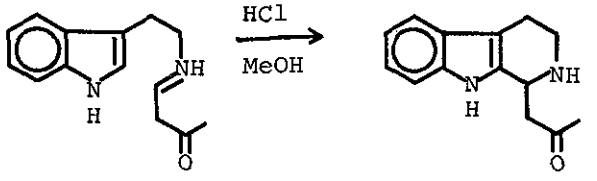
XVI XVII (10)



(11)

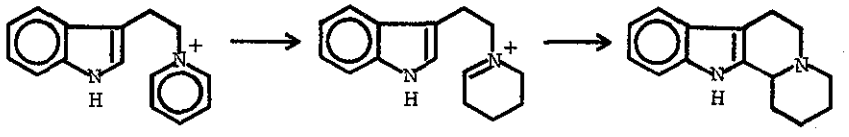
In addition, β-keto-aldehydes and tryptamine hydrochloride have also been condensed to form β-carbolines (Eq 12) (27).



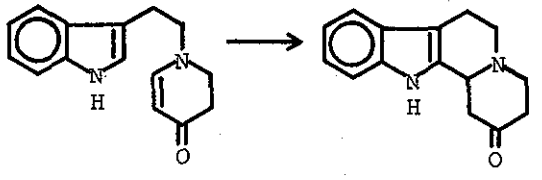


(12)

The formation of an imminium ion from the Schiff base promotes the cyclization; therefore the equilibria between enamine and imine tautomers can also be utilized to prepare tetracyclic derivatives (3) as shown in Eq 12, 13 (28), and 14 (22).



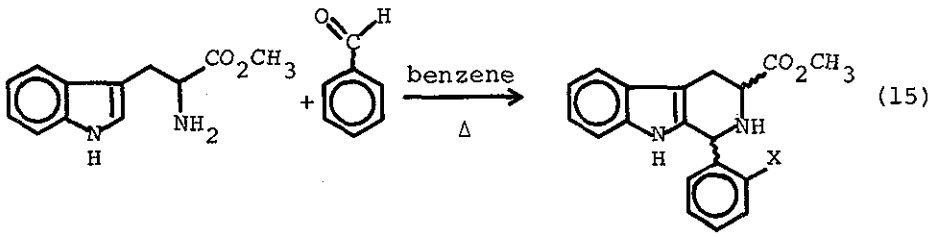
(13)



(14)

The most recent advance regarding the conditions of the Pictet-Spengler reaction was reported in 1976 (29). When tryptamine and

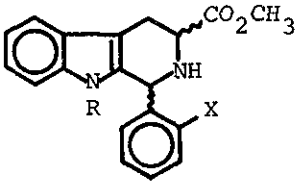
aldehydes were refluxed in an aprotic solvent only the Schiff base was formed; however, when the same aldehydes were heated either with tryptophan methyl ester or N_b-benzyltryptamine in aprotic solvents, tetrahydro-β-carbolines were formed in good yield. For example, 1-phenyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline (XVIIIa) was prepared in 90% yield by heating tryptophan methyl ester and benzaldehyde in refluxing benzene (Eq 15) (29).



(15)

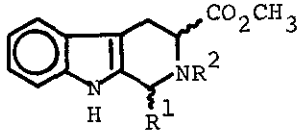
XVIIIa, X = H

This modification has led to improved synthesis of several tetrahydro-β-carbolines including the phenol (XVIIIb), the tryptophan methyl ester derivatives (XVIIIc-e) and the diethyl-acetal products (XVIIIf and g) (29b). An explanation for these facile cyclizations has been presented (29b). This methodology has also been employed to prepare the antibiotic, pyridindolol XVIIIh (29c), for attempts to prepare this β-galactosidase inhibitor via the usual reactions in aqueous acid were not successful (29d).



XVIIIa, X = H

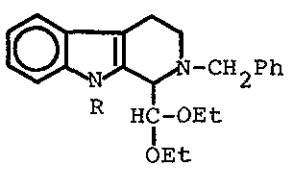
XVIIIb, X = OH



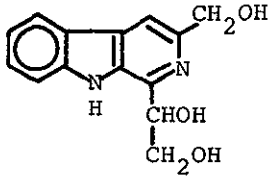
XVIIIc, $R^1 = CH_2CH_2CO_2CH_3$, $R^2 = CH_2Ph$

XVIIId, $R^1 = CH(OEt)_2$, $R^2 = CH_2Ph$

XVIIIe, $R^1 = CH(OEt)_2$, $R^2 = H$



XVIIIf, R = CH_3



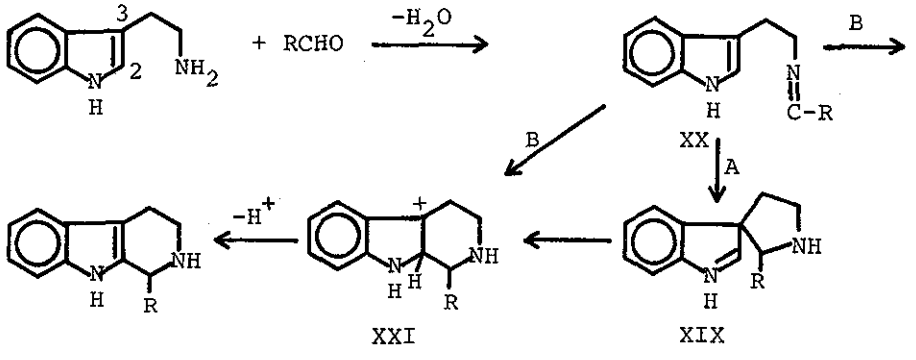
XVIIIh

XVIIIg, R = H

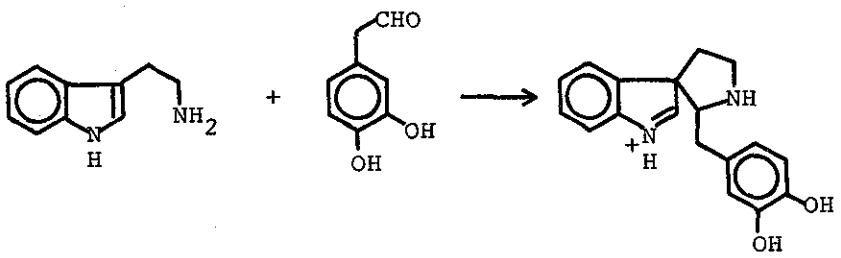
The Spiroindolenine Intermediate

There are two principal mechanistic pathways which have been proposed for the Pictet-Spengler condensation: the spiroindolenine route (Scheme 2, path A), which is thought to arise by electrophilic attack of the Schiff base XX at the three position of the indole, followed by a 1,2 alkyl shift to form the intermediate XXI; or the simpler pathway which involves the direct formation of the cationic intermediate XXI by electrophilic attack of the Schiff base XX at the two position of the indole (Scheme 2, path B). Reports about either of these two mechanisms have appeared in several journals and, in general, strongly implicate the spiroindolenine intermediate XIX as the central step in this reaction.

SCHEME 2



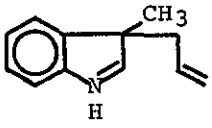
In 1948, Woodward (30) proposed the spiroindolenine as an intermediate for the biosynthesis of Strychnos alkaloids (Eq 16).



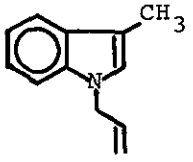
(16)

This appears to be the origin of the spiroindolenine hypothesis. Within the last decade, Jackson and coworkers have reported a substantial amount of evidence in support of the spiroindolenine *mechanism stemming* from investigations of the electrophilic reactivity of the 2,3-indole double bond.

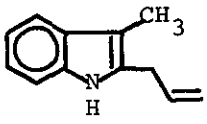
Initially, Jackson and Smith (31) reported that reaction of 3-methylindolylmagnesium iodide and allyl bromide resulted in the products XXII-XXIV. In dilute acid the indolenine XXII rearranged



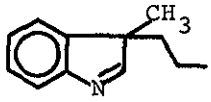
XXII, 44%



XXIII, 4%



XXIV, 28%

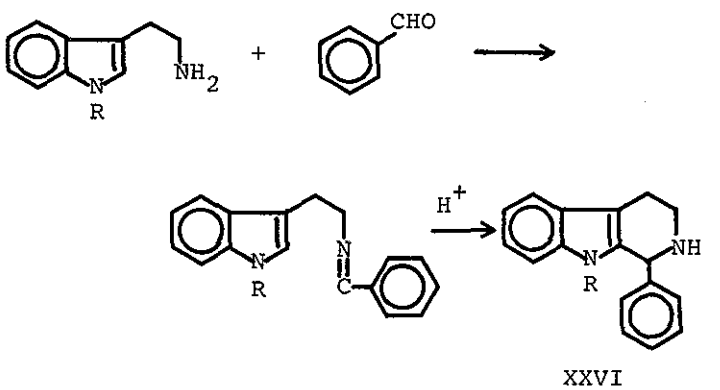


XXV

to the 1,2-disubstituted indole XXIV; however, the thermal rearrangement (XXII → XXIV) did not take place. Stronger conditions (6 N

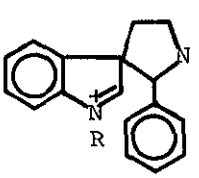
acid, heat) were needed to rearrange 3-methyl-3-propylindolenine (XXV) while the N-alkylated indole (XXIII) would not rearrange to the 1,2-disubstituted indole (XXIV) either under acidic or thermal conditions.

Having noted that Hoshino and Kotake (32) had synthesized 1-phenyl-1,2,3,4-tetrahydro-β-carboline (XXVI, R = H) from tryptamine and benzaldehyde in an acidic (EtOH/HCl) medium (Eq 17), Jackson and Smith (33) attempted to trap the spiroindolenine intermediate (XXVII, R = H). They reported that even under



(17)

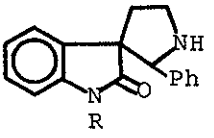
XXVI



XXVII

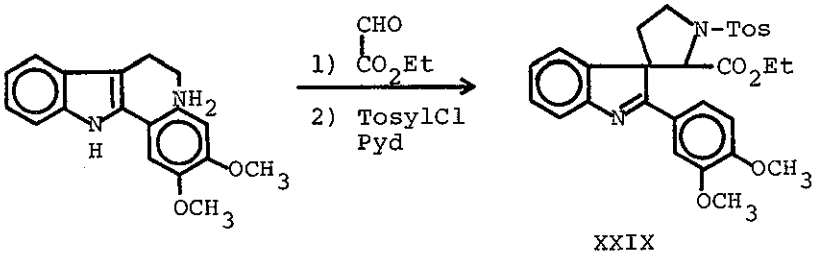
extremely mild acid conditions (dry HCl in ether) the tetrahydro-β-carboline (XXVI, R = H) resulted immediately, and quantitatively, instead of the indolenine (XXVII, R = H). A similar result was found in the N_a-methyl (XXVI, R = CH_3) case. In this same series

at pH 8 only starting materials were isolated, and at high temperatures or higher pH, hydrolysis resulted. Attempts to trap the spiroindolenine by oxidation to the spirooxindole (XXVIII, R = H) with ferricyanide (under both neutral and alkaline conditions)



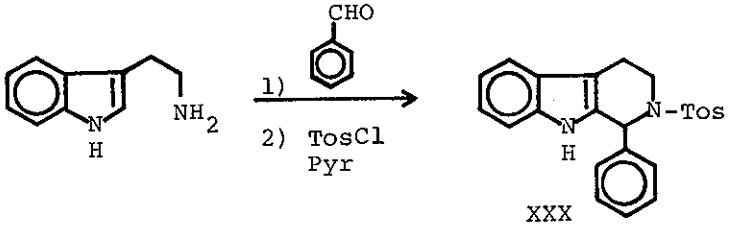
XXVIII

failed. Jackson and Smith (33), however, also noted that Woodward (34) had reported the formation of a spiroindolenine (XXIX) in the synthesis of strychnine, when p-toluenesulphonyl chloride in



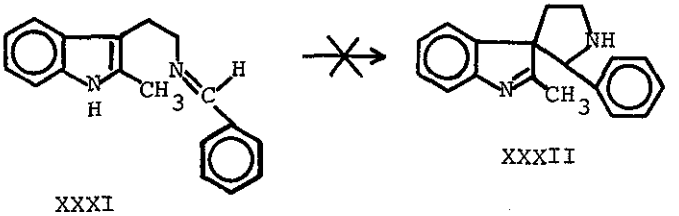
XXIX (18)

pyridine was employed to cyclize the Schiff base (Eq 18). The benzylidene derivative of tryptamine, however, was transformed into the N_b-tosyl-tetrahydro-β-carboline (XXX) when Woodward's procedure was attempted (Eq 19). Furthermore, 2-methylbenzylidene



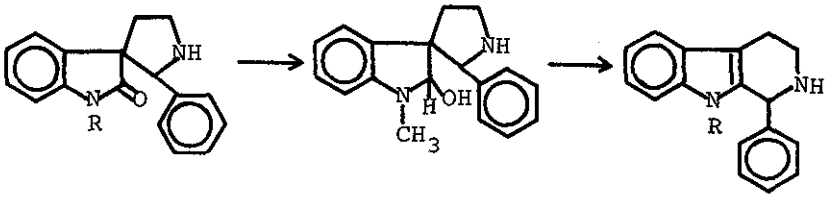
XXX (19)

tryptamine (XXXI) also did not react to form the spiroindolenine (XXXII) under these same conditions (Eq 20).



XXXI XXXII (20)

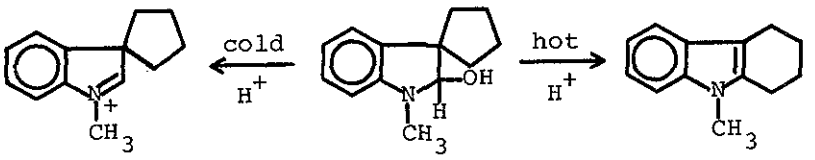
To investigate the suspected rearrangement of the spiroindolenine, the oxindole (XXVIII, R = CH_3) was synthesized (33). Lithium aluminum hydride reduction of XXVIII (R = CH_3) provided the carbinolamine (XXXIII), which underwent facile rearrangement to the tetrahydro-β-carboline (XXVI, R = CH_2) even in spectroscopic grade ethanol (Eq 21). To avoid rearrangement of the



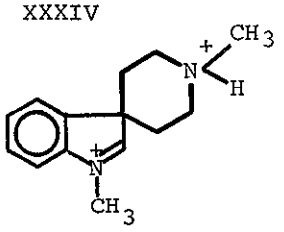
XXVIII XXXIII XXVI (21)

carbinolamine (XXXIII), it was necessary to store the material in alkaline solution for the slightest trace of acid induced rearrangement. The carbinol (XXXIV) had been synthesized earlier by Witkop and Patrick (35), from the corresponding oxindole. Jackson and Smith (33) reported that this compound (XXXIV) formed the spiroindolenine (XXXV) in cold acid, but rearranged to the carbazole (XXXVI) in hot acid (Scheme 3). The quaternary amine

SCHEME 3



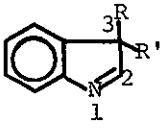
XXXV XXXIV XXXVI



XXXVII

(XXXVII) had also been synthesized by Jackson and Smith (23) from the corresponding oxindole, and this salt was found to be very stable even in phosphoric acid (180°C for 4 hours).

Continuing their investigation, Jackson and Smith (36) next studied the migratory aptitude of various groups attached to the three position of the indolenine (XXXVIII). The order of migratory

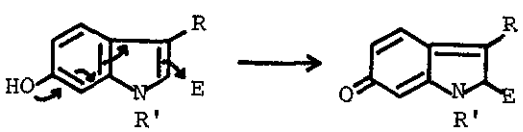


XXXVIII

aptitudes (33,36) was CH_3 < CH_3CH_2 < i-Pr < Allyl < $PhCH_2$ < $PhCH\text{-}NR_2$. Kinetic studies (no data given) indicated that the rearrangement was first order when sufficient acid was present to completely protonate the indolenines. The actual rearrangement was thought to be of the "Wagner-Meerwein" type, since no "cross-over" products

were found when 3,3-dimethyl and 3,3-diethyl indolenines were rearranged in the same solution. Attempts to prepare optically active indolenines (XXXVIII, R' = *sec* octyl, $Ph(CH_3)CH$- and R = CH_3) to expand this investigation failed, apparently due to steric effects.

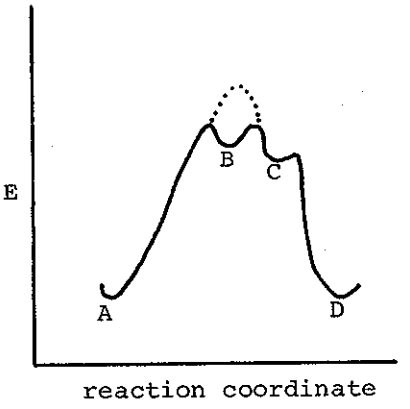
The energy diagram (Fig. 1) described by Jackson *et al.* (37) illustrates the two possible pathways for electrophilic attack on 3-substituted indoles. The disruption of the resonance energy of the benzene ring (Fig. 1, path 2) they stated, should require more energy than the formation of the corresponding indolenine (Fig. 1, path 1), which upon rearrangement would result in the same intermediate (C). Therefore, attack at the indole-3-position should be favored over attack at the indole-2-position. Furthermore, the final step, the loss of the proton to rearomatize the ring, would be rapid and not influence the interpretation of the mechanism. The energy barrier for attack at the two position of indole (path 2) may become competitive with the indolenine mechanism (path 1) if there are changes in the substrate or reaction conditions. For example, the 6-hydroxyindole (XXXIX) may donate electrons to stabilize the intermediate (Eq 22); Casuati, Dossena and Pochini



(22)

XXXIX

(38) have shown that direct attack at the indole-2-position (path 2) does take place under some circumstances (see below). It



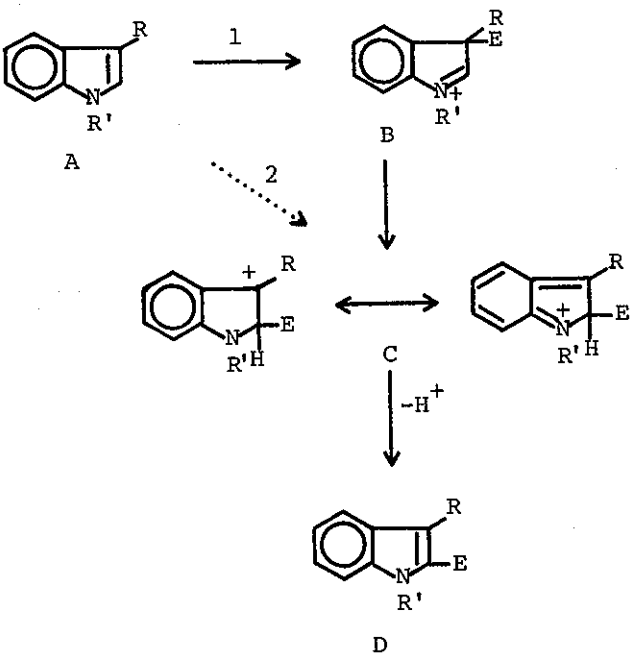
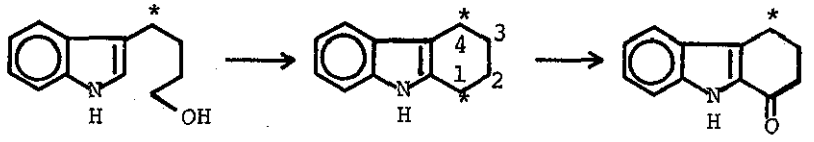


Figure 1. The dashed line represents route 2 (direct attack at 2-position of indole). The solid line represents route 1 (indolenine mechanism).

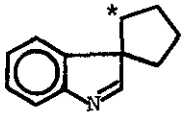
appears reasonable that the indolenine may be the kinetically controlled product while the rearranged 2,3-disubstituted indole is the thermodynamically controlled product; especially since vigorous conditions are required to rearrange a tetrahydro-β-carboline to a spiroindolenine (39).

An important experiment in the investigation of the mehcanism was the synthesis of indolyl-3-butanol (XL) with a tritium label on the methylene group adjacent to the indole ring [Jackson, Naidov and Smith (37)]. Using BF_3-etherate, the indolyl-3-butanol (XL) was cyclized to the tetrahydro-β-carbazole (XLI), which still contained all of the tritium label. The carbazole (XLI) was oxidized to the 1-oxo derivative (XLII) (Eq 23). Upon examination, half of the label had been lost in the formation of the 1-oxo



XL XLI XLII (23)

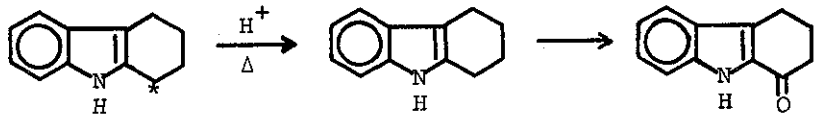
derivative (XLII); it was concluded that the label was equally distributed between the one and four positions of the carbazole (XLI). This scrambling could have only resulted through the spiroindolenine (XLIII). The possibilities for exchange



XLIII

or reequilibration after cyclization were tested, for it is possible

to rearrange tetrahydrocarbazoles to spirocyclic indolenines in strong acid (39). Therefore, the carbazole (XLIV) with tritium label only at the 1-position was heated in strong acid. Loss of tritium label resulted and no tritium label was found at the carbazole-4-position (Eq 24); consequently, the scrambling could

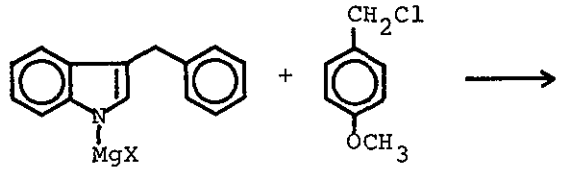


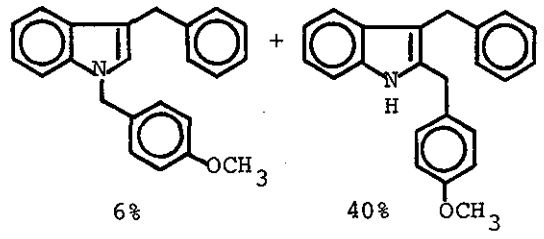
(24)

XLIV

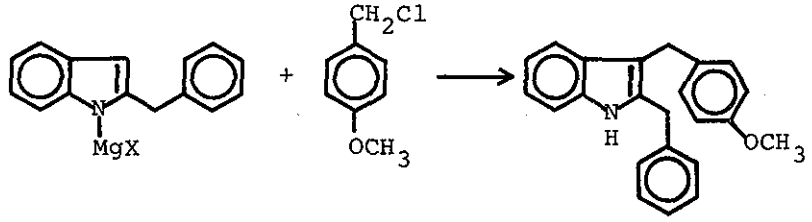
not have occurred by the equilibration of the carbazole but only by the formation of the indolenine (XLIII).

Biswas and Jackson (40) investigated the indole Grignard reactions illustrated below (Eq 25-27). It is apparent that the

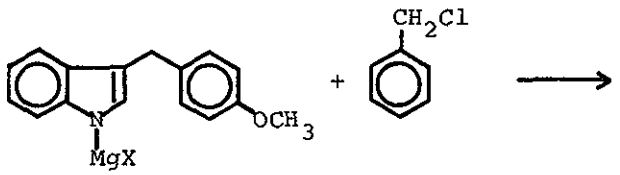


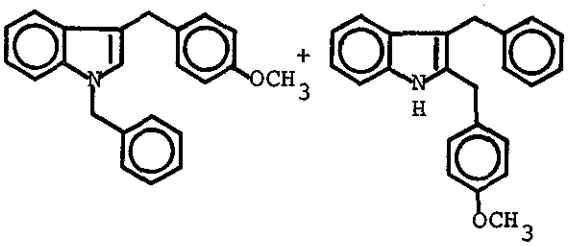


(25)



(26)

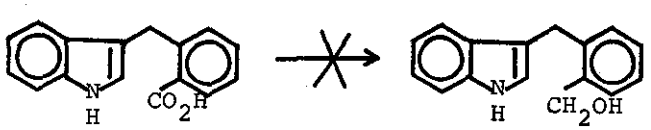




16% 71%

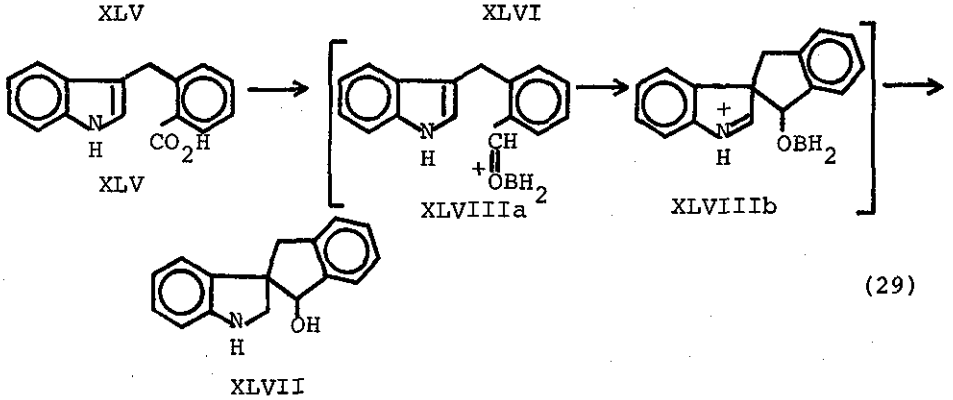
(27)

indolenine intermediate must have formed, since the p-methoxybenzyl group migrates preferentially (Eq 27) to the indole-2-position. Also in this study a more important result was found which strongly supports the spiroindolenine mechanism. In the diborane reduction of the carboxybenzylindole (XLV), the expected alcohol (XLVI) was not formed (Eq 28); instead, the spiroindoline (XLVII) was obtained (Eq 29), presumably through the intermediates



XLV XLVI

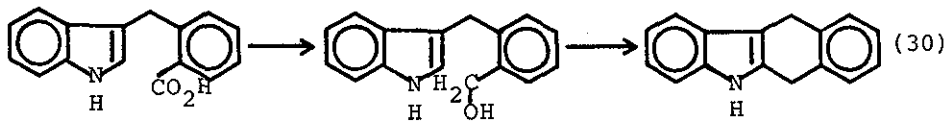
(28)



XLV XLVIIIa XLVIIIb XLVII

(29)

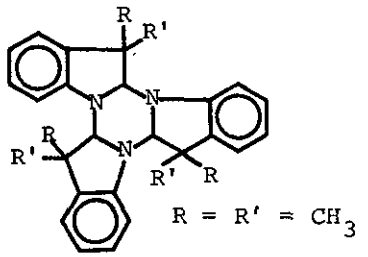
XLVIIIa and XLVIIIb. In a parallel investigation the alcohol (XLVI) was formed from the carboxybenzylindole (XLV) by lithium aluminum hydride reduction, and was condensed to provide the tetracyclic derivative (XLIX) (Eq 30). Isolation of the spiro-



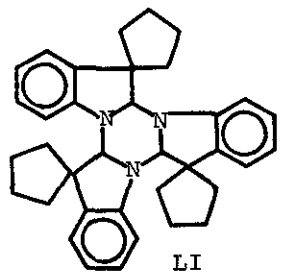
XLV XLVI XLIX

indolenine derivative XLVII from the reduction (Eq 29) provided strong evidence for the spiroindolenine mechanism for the intermediate XLVIIIb had been trapped (Eq 29) by reduction of the indole-1,2-double bond (XLVIIIb) before rearrangement could take place. The desired compound (XLIX) was later obtained by employing a slower reducing agent in the first step, as shown in Eq 30.

In 1953, Witkop and Patrick (35) noted that 3,3-dimethylindolenine forms a trimer in refluxing benzophenone or acetic anhydride. Jackson and coworkers (31,33,36,41) investigated the structures of these trimers. In the crystalline state, neutral or alkaline conditions, the indolenines existed as trimers (L). In addition, the spiroindolenine of indolylbutanol existed as the trimer (LI) in both deuterochloroform and the solid state. Treatment

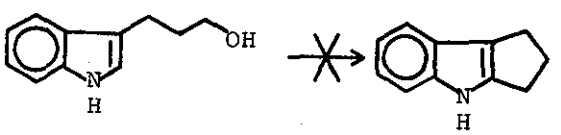


L



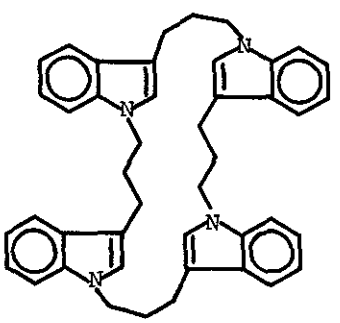
LI

with acid immediately cleaved the trimer and slow cyclization to the tetrahydrocarbazole (XLI) followed. When indolyl-3-propanol (LII) was reacted in BF_3-etherate to form the tricyclic indole LIII only polymer resulted (Eq 31). In a similar study the tosylate



LII LIII (31)

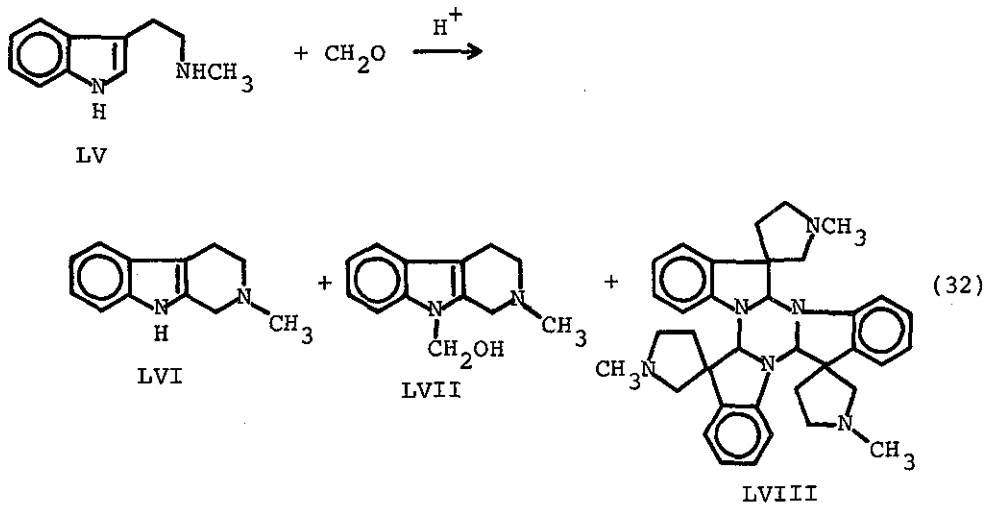
of indolyl-3-propanol (LII) was stirred with potassium t-butoxide in t-butanol to give the tetramer (LIV). In neither case was any



LIV

of the tricyclic compound isolated. In a similar vein strong evidence for the spiroindolenine mechanism was reported in a paper by Ghosal and Banerjee (18). Abrine (LV) and formaldehyde were reacted in strong acid (pH < 2) to give a mixture of three products (LVI-LVIII) (Eq 32). In other cases polymeric materials resulted, but only in the case of LV was any of the polymeric material identified.

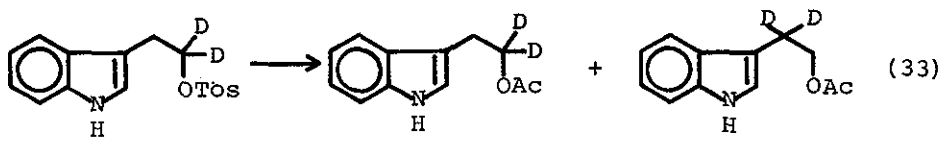
The significant point is that a portion of the spiroindolenine



LV LVI LVII LVIII (32)

intermediate trapped itself in the form of the trimer (LVIII), while the rest of the material rearranged to form the tetrahydro-β-carbolines (LVI and LVII).

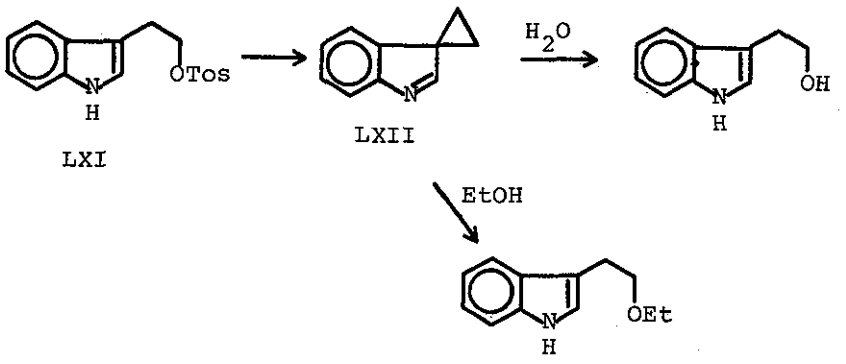
Acetolysis of the deuterated tosylate (LIX) was studied by Closson *et al.* (42). A 50:50 mixture (by NMR) of the two deuterated acetates (LXa and LXb) were found (Eq 33). When the tosylate (LXI)



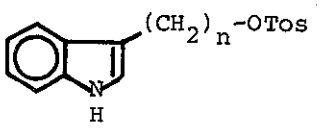
LIX LXa LXb (33)

was reacted with potassium t-butoxide in THF (under N_2), the *spiroindolenine* (LXII) was found and was easily hydrolyzed with either water or ethanol (Scheme IV). Jackson and Naidov (41) carried out a similar investigation to determine the solvolysis rates of the tosylates (LXIIa-d). This study indicated that the

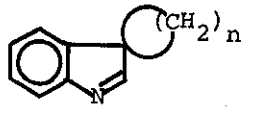
SCHEME 4



indole double bond does participate in the solvolysis; the order was found to be a > c > d > b. This order parallels Winstein's (43) studies on neighboring group effects in simple benzenoid systems. It is important to note that the solvolysis rate of indolylethyl tosylate (LXIIIa) was about 1000 times faster than the solvolysis rate of the corresponding ethyl tosylate. Also, the rates of solvolysis of LXIIIb and d were about the same, but LXIIId formed only a trace of cycloheptindole. The type of participation, apparently, involves the spiroindolenines LXIVa-d;



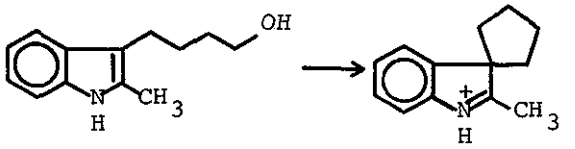
LXIIIa, n = 2
b, n = 3
c, n = 4
d, n = 5



LXIVa, n = 2
b, n = 3
c, n = 4
d, n = 5

moreover, three- or five-membered spiroindolenines formed easier than their four- or six-membered counterparts. Furthermore,

Jackson and Naidoo (44) were able to cyclize 2-methylindolyl-butanol (LXV) to the spiroindolenine (LXVI) with BF_3-etherate (Eq 34). The corresponding tosylate also formed the spiroindolenine

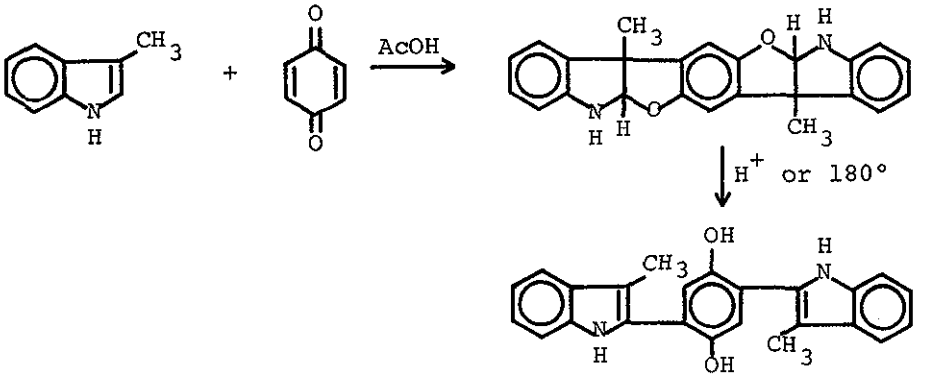


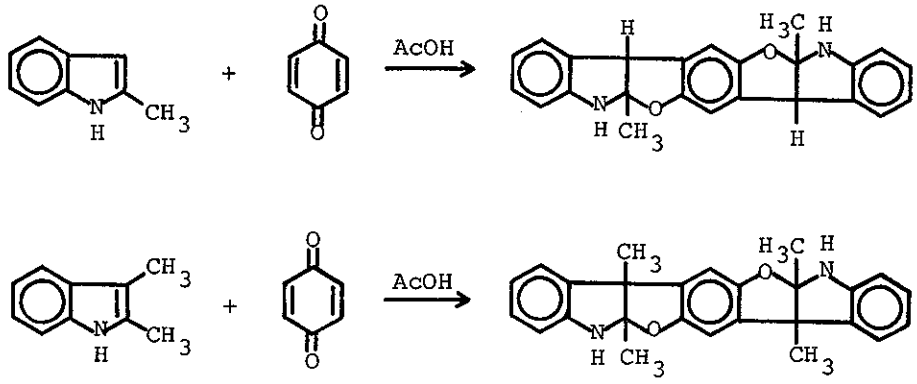
LXV LXVI (34)

(LXVI) on treatment with potassium t-butoxide or on passage through a column of alumina.

In 1958, Noland and Robinson (45) published a report which indicated that 2,3-dimethylindole would not react with benzaldehyde as did 2-methyl- and 3-methylindole. For this reason, they concluded that the mechanism must be direct attack at the two-position of indole. In 1966, however, Noland and Bande (46) subsequently reported results that did support the indolenine mechanism. These findings are shown in Scheme 5.

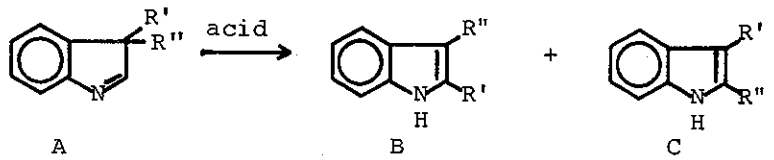
SCHEME 5





As mentioned earlier, Casnati *et al.* (38) have shown that direct attack at the two-position of indole can occur under the right conditions. Their results are shown in Tables 1 and 2.

TABLE 1

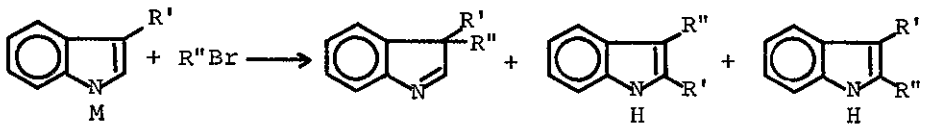


A B C

R'	R"	CF_3CO_2H B(%)	CF_3CO_2H C(%)	CH_3CO_2H/NaOAc B(%)	CH_3CO_2H/NaOAc C(%)	$MgBr_2$ B(%)	$MgBr_2$ C(%)
$C_6H_5CH_2$	CH_2=$CHCH_2$	100	--	--	--	100	--
$(CH_3)_2C$=$CHCH_2$	CH_2=$CHCH_2$	100	--	--	--	100	--
$(CH_3)_2C$=$CHCH_2$	CH_3CH=$CHCH_2$	90	10	85	15	82	18
$C_6H_5CH(CH_3)$	$C_6H_5CH_2$ (+)	80	20	--	--	90	10
$C_6H_5CH(CH_3)$	$C_6H_5CH_2$ (-)	98	2	--	--	95	5

(+) and (-) indicate relative R_f's for the diastereomers.

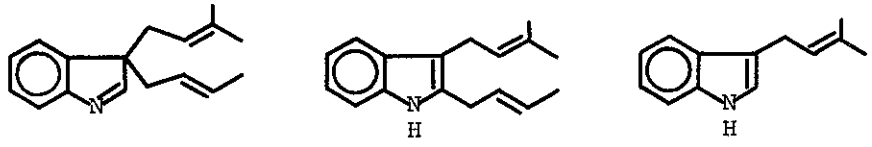
TABLE 2



M D E F

M	R'	R"	Solvent	D + E(%)	F(%)
MgBr	$C_6H_5CH_2$	$CH_2=CHCH_2$	Et_2O	63	37
MgBr	$C_6H_5CH_2$	$CH_2=CHCH_2$	THF	100	--
MgBr	$(CH_3)_2C=CHCH_2$	$CH_2=CHCH_2$	Et_2O	87	13
MgBr	$(CH_3)_2C=CHCH_2$	$CH_3CH=CHCH_2$	Et_2O	58	42
MgBr	$C_6H_5CH(CH_3)$	$C_6H_5CH_2$	Et_2O	78	22
H	$(CH_3)_2C=CHCH_2$	$CH_3CH=CHCH_2$	CH_3CO_2H/NaAc	49	51

In Table 2 the increase in amount of indole (F) produced, compared to the same compound formed under the conditions which are underlined in Table 1, can only be explained by direct attack at the indole two position. For example, the indolenine (LXVII) listed in Table 1 gave only 15% of the indole (LXVIII) after rearrangement in acetate buffer; whereas, the reaction of the 3-substituted indole (LXIX) with 3-bromo-2-butene produced 51% of the indole (LXVIII) in the same medium. The additional amount (36%) of the

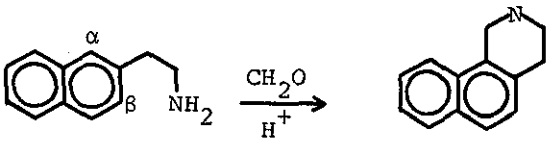


LXVII LXVIII LXIX

indole (LXVIII) isolated can only be from the direct attack at the two position, since only 15% could be accounted for by

rearrangement of the indolenine (LXVII). It is important to mention that when the solvent is changed from ether to THF (Table 2), none of the indole (LXVIII) was produced. Casnati's results indicate that direct attack at the 2-position can become competitive with the alkylation at position 3 in 3-alkylindoles depending on steric effects, halide reactivities and reaction conditions. This illustrates that certain reaction parameters can be altered to provide more attack at the 2-position of indole.

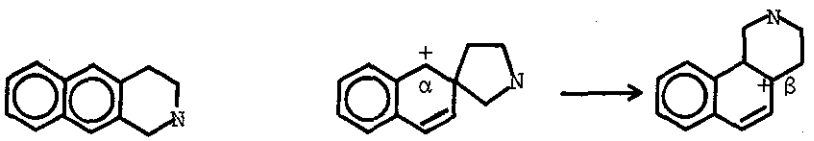
In 1923, Mayer and Schnecko (17) reported that when β-ethylaminonaphthalene (LXX) and formaldehyde were condensed in acid, only the product of cyclization in the α-direction (LXXI) was



(35)

LXX LXXI

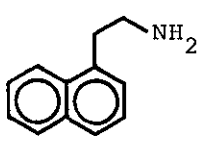
formed and none of the β-isomer (LXXII) was isolated. The spiroindolenine intermediate (LXXIII) could be employed to explain this phenomenon; once the β-spiroindolenine (LXXIII) has formed, the



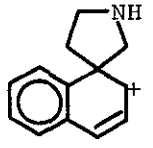
LXXII LXXIII LXXIV

positive charge rests on the less stable α-position (48). Rearrangement would then move the positive charge to the more stable β-position (48) (LXXIV) and this would act as the driving force for this reaction. When α-ethylaminonaphthalene (LXXV) was reacted

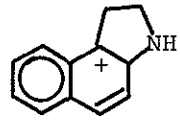
under the same conditions, no reaction took place. Apparently, if the α-spiroindolenine (LXXVI) did form, there would be a negative driving force (against rearrangement), since the rearrangement would result in the formation of a less stable carbonium ion (LXXVII). Furthermore, since no "peri" product (LXXVIII) was found,



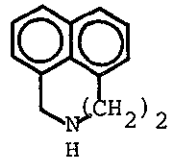
LXXV



LXXVI

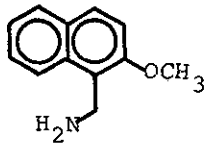


LXXVII

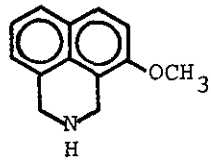


LXXVIII

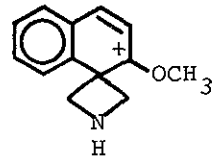
direct attack can be ruled out. In a related investigation Dey and Rajagopolar (49) subjected 1-aminomethyl-2-methoxynaphthalene (LXXIX) to reaction under analogous conditions to that described above. Again, no "peri" product (LXXX) was isolated even through the "peri" position was activated by a methoxy group. The



LXXIX



LXXX



LXXXI

above two examples suggest that the spiroindolenine intermediate could well be occurring in systems much different than indole.

There is more evidence available to support the spiroindolenine mechanism for the Pictet-Spengler reaction in the case of tetrahydro-β-carbolines. The reader is referred to reference 50 for other work in the area.

References and Notes

[1]W. Whaley and T. Govindochari, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, 1951, p. 74.

[2]Ibid., p. 151.

[3]R. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, p. 236.

[4]R. Abramovitch and I. Spenser, "Advances in Heterocyclic Chemistry," Vol. 3, Academic Press, New York, 1964, p. 79.

[5]W. Kermack and J. McKail, "Heterocyclic Compounds," Vol. 7, John Wiley and Sons, Inc., New York, 1961, p. 237.

[6]K. Stuart and R. Woo-Ming, Heterocycles, 1975, 3, 223.

[7]A. Pictet and T. Spengler, Ber., 1911, 44, 2030.

[8]M. Konda, T. Oh-ishi, and S. Yamada, Chem. Pharm. Bull., 1977, 25, 69; M. Konda, T. Shioiri, and S. Yamada, ibid., 1975, 23, 1063; E. Yamato, ibid., 1970, 18, 2038; T. Kametani, K. Fukumoto, and T. Katagi, ibid., 1959, 7, 567.

[9]Tatsui, J. Pharm. Soc. Japan, 1928, 48, 92, referenced from reference 2.

[10]S. Akabori and K. Saito, Ber., 1930, 63, 2245.

[11]J. Bergman, Acta Chem. Scand., 1971, 25, 3296.

[12]M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., J. Med. Chem., 1964, 7, 141; U. S. Pat. 3,304,309 (1967).

[13]J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, J. Med. Chem., 1967, 10, 127.

[14]A. Brossi, A. Focella, and S. Teitel, J. Med. Chem., 1973, 16, 418.

[15]M. Julia and J. Lallemand, Bull. Soc. Chim., 1973, 6, 2058.

[16]M. Julia, J. Bagot, and O. Siffert, Bull. Soc. Chim., 1973, 4, 1424.

[17]R. Brown and C. Chapple, Chem. Comm., 1973, 886.

[18]S. Ghosal and P. K. Banerjee, Ind. J. Chem., 1971, 9, 289.

[19]R. N. Schut, U. S. Pat. 3,413,293 (1968).

[20]J. Gootjes and W. Nauta, Recueil, 1966, 85, 966.

[21]J. Knabe and R. Suggau, Arch. Pharmaz., 1973, 306, 500.

[22]E. Winterfeldt, Ber., 1964, 97, 2463.

[23]J. B. Hester, Jr., J. Org. Chem., 1964, 29, 2864.

[24]N. Carrasco, A. Urzua, and B. K. Cassels, J. Org. Chem., 1973, 38, 4342.

[25]G. B. Kline, J. Am. Chem. Soc., 1959, 81, 2251.

[26]S. Archer, U. S. Pat. 3, 468,890 (1969).

[27]R. N. Schut, Chem. Ind., 1960, 1246.

[28]J. Thesing and W. Festag, Experienta, 1959, 15, 127.

[29](a) J. Sandrin, D. Soerens, L. Hutchins, L. Richfield, F. Ungemach, and J. M. Cook, Heterocycles, 1976, 4, 1101; (b) J. Sandrin, D. Soerens, P. Mokry, and J. M. Cook, Heterocycles, 1977, 6, 1133; (c) G. Wu, E. Yamanaka, and J. M. Cook, Heterocycles, 1978, 9, 175; (d) F. Hamaguchi and S. Ohki, Heterocycles, 1977, 8, 383.

[30]R. B. Woodward, Nature, 1948, 162, 155.

[31]A. H. Jackson and A. E. Smith, Tetrahedron, 1965, 21, 989.

[32]T. Hoshino and Y. Kotake, Liebigs Ann., 1935, 516, 76.

[33]A. H. Jackson and A. E. Smith, Tetrahedron, 1968, 24, 403.

[34]R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, Tetrahedron, 1963, 19, 247.

[35]B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 1953, 75, 2572.

[36]A. H. Jackson and P. Smith, Tetrahedron, 1968, 24, 2227.

[37]A. H. Jackson, B. Naidoo, and P. Smith, Tetrahedron, 1968, 24, 6119.

[38]G. Casnati, A. Dossena, and A. Pochini, Tetrahedron Lett., 1972, 52, 5277.

[39]J. Harley-Mason and W. R. Waterfield, Tetrahedron, 1963, 19, 65; J. Harley-Mason, Chem. Comm., 1965, 248; J. Harley-Mason and M. Kaplan, ibid., 1967, 915.

[40]K. M. Biswas and A. H. Jackson, Tetrahedron, 1969, 25, 227.

[41]A. H. Jackson and B. Naidoo, Tetrahedron, 1969, 25, 4843.

[42]W. D. Closson, S. A. Roman, G. T. Kwiatkowski, and D. A. Corwin, Tetrahedron Lett., 1966, 2271.

[43]R. Heck and S. Winstein, J. Am. Chem. Soc., 1957, 79, 3105, 3114; R. Baird and S. Winstein, ibid., 1957, 79, 756, 4238; and 1963, 85, 567.

[44]A. H. Jackson and B. Naidoo, J. C. S. Perkins II, 1973, 548.

[45]W. E. Noland and D. N. Robinson, Tetrahedron, 1958, 3, 68.

[46]W. E. Noland and F. J. Baude, J. Org. Chem., 1966, 31, 3321.

[47]F. Mayer and O. Schnecke, Ber., 1923, 56, 1408.

[48]R. Morrison and R. Boyd, "Organic Chemistry," 3rd ed., Allyn and Bacon, Inc., Boston, 1973, p. 978.

[49]Dey and Rajagopalar, Arch. Pharm., 1939, 277, 377, referenced from reference 2, p. 160.

[50]E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, Tetrahedron Lett., 1960, 19, 30; H. J. Anderson and L. C. Hopkins, Can. J. Chem., 1964, 42, 1279; T. F. Spande, M. Wilchek, and B. W. Witkop, J. Am. Chem. Soc., 1968, 90, 3256; G. M. London and D. E. Koshland, Jr., J. Biol. Chem., 1970, 245, 2247; E. E. van Tamelen, J. Webber, G. P. Schiemenz, and W. Barker, Bioorg. Chem., 1976, 5, 283.

Received, 7th June, 1978