A DEVELOPMENT OF PICTET-SPENGLER REACTION IN APROTIC MEDIA USING CHLOROFORMATES; A SHORT SYNTHESIS OF BORRERINE

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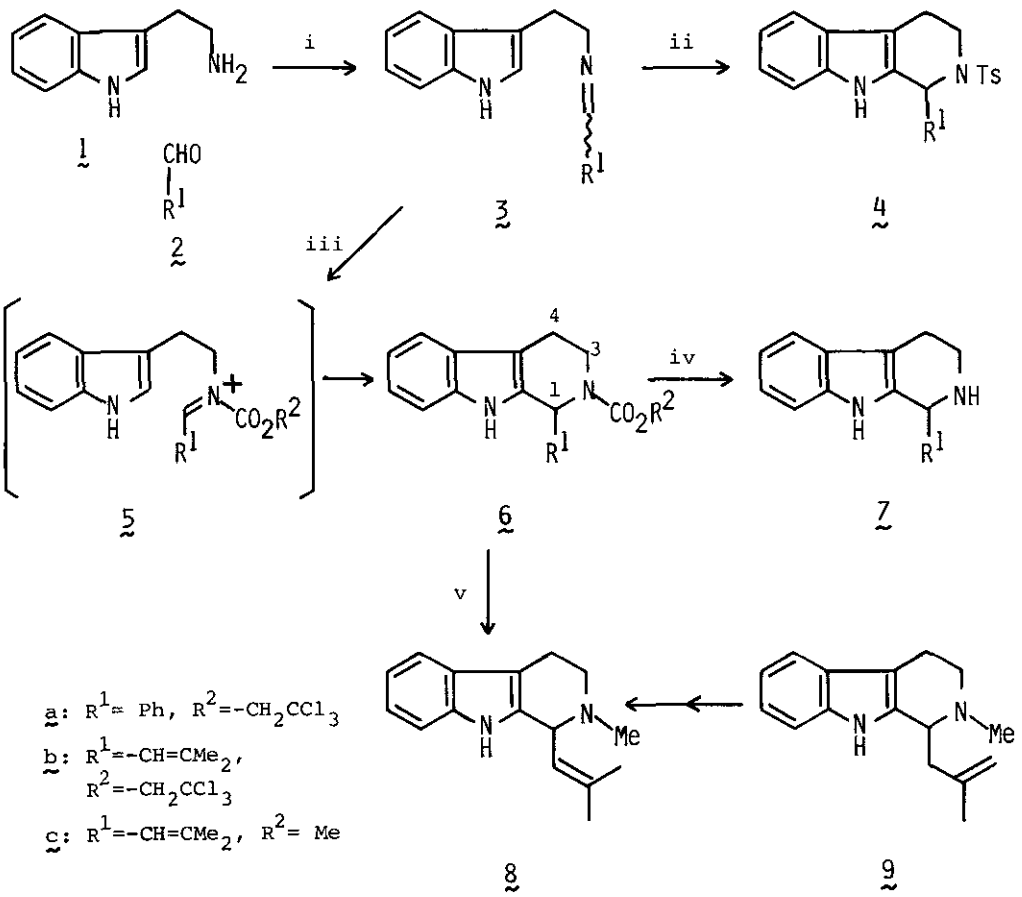
Abstract —— Pictet-Spengler reaction between tryptamine (1) and aldehydes (2a,b) was achieved through the intermediates (5a,b,c) in the presence of chloroformates to give the β-carbolines (6a,b,c), which were converted to the amines (7a,b) and the natural alkaloid, borrerine (8).

A development of Pictet-Spengler (P-S) reaction in refluxing aprotic solvents (benzene, toluene, xylene) was recently made by Cook[1] using tryptophan derivatives and Nb-benzyltryptamine. P-S reaction of Nb-benzylidenetryptamine (3a) did not occur under the same condition[1], while the reaction proceeded to the β-carboline (7a) in the presence of acids.[2,3] The conversion of the imine (3b) to the P-S product (7b) was also unsuccessful even in the presence of acids.[4]
P-S reaction of the imines 3a and 3b with *p*-toluenesulfonyl chloride in pyridine was reported to give the tosylates 4a[2] and 4b[4], respectively.
We thought that P-S reaction of the imine (3) should proceed with chloroformates instead of TsCl through the intermediate (5) to give the carbamate (6), which could be converted to the amine (7) by removal of Nb-alkoxycarbonyl group or to Nb-methyl compound (*e.g.* 8) by $LiAlH_4$ reduction.
We wish to report here a development of P-S reaction in aprotic media using chloroformates and a short synthesis of borrerine (8)[5], which was recently synthesized by the isomerization of double bond of isoborrerine (9).[6]
Isoborrerine (9) had been synthesized in several steps.[7)]
The imine (3a)[2] was treated with trichloroethyl chloroformate (1.1 eq) in dry CH_2Cl_2 in the presence of pyridine (2 eq) at room temperature to give the β-carboline (6a) [68%; mp 142-144°C(benzene-hexane); m/z(%): 424(M^++2,18), 422



a: R^1= Ph, R^2=-CH_2CCl_3

b: R^1=-CH=CMe_2, R^2=-CH_2CCl_3

c: R^1=-CH=CMe_2, R^2= Me

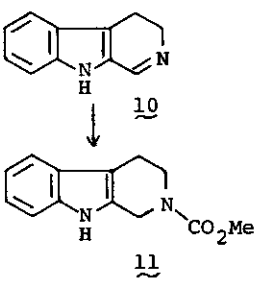
i) Molecular sieves 4A/ CH_2Cl_2 ii) TsCl/pyridine

iii) $ClCO_2R^2$-pyridine/ CH_2Cl_2 iv) Zn/ AcOH v) $LiAlH_4$/ THF

Table. ^{13}C Chemical Shifts of Carbamates

carbon	6a	6b	6c	11
1	55.1	50.4	49.9	42.3[a]
3	38.9	39.9	39.4	42.2[a]
4	21.6	21.5	21.5	21.3

[a] Values may be interchanged.



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11

(M^+,17), 244(100); ^{1}H-NMR δ: 4.82(2H,AB q,J=12Hz,O$\underline{CH_2}$CCl$_3$), 6.48(1H,br s,H-1)].[8]

The removal of alkoxycarbonyl group of 6a was made by treatment with Zn in AcOH to give the amine (7a; 71%; mp 165-166°C), which was identical with the authentic sample prepared by the reported manner.[2]

Next, one-pot reaction of tryptamine (1) and benzaldehyde (2a) to the β-carboline (6a) was attempted without isolation of the imine (3a). The mixture of 1 (2 mmol) and 2a (2.1 mmol) in dry CH_2Cl_2 (10 ml) in the presence of molecular sieves 4A (5 g) was stirred overnight at rt. After addition of pyridine (4 mmol) to the mixture, the chloroformate (R^2=CH_2CCl_3,2.2 mmol) was added dropwise under ice cooling. After stirring for 3-5 h at rt, the mixture was filtered. The filtrate was washed with N HCl and H_2O successively, and dried. The crude products were chromatographed on silica gel to give the β-carboline (6a; 67%).

P-S reaction using chloroformates was found to proceed smoothly though the yield was moderate, and the present method was applied to the imine (3b), which could be prepared from tryptamine (1) and 3-methyl-2-butenal (2b).[4]

One-pot reaction of 1 and 2b with trichloroethyl and methyl chloroformates as described above gave the β-carbolines 6b and 6c, respectively[6b: 56%; mp 175-176°C(MeOH); m/z(%): 402(M^++2,27), 400(M^+,28), 269(100); ^{1}H-NMR δ: 1.78(3H,d, J=1.3Hz,=C$\underline{Me_2}$), 2.00(3H,d,J=1.3Hz,=C$\underline{Me_2}$), 4.81(2H,br s,O$\underline{CH_2}$CCl$_3$), 5.39(1H,d like, J=9.5Hz,-$\underline{CH}$=CMe$_2$), 5.99(1H,d,J=9.5Hz,H-1). 6c: 68%; mp 180-181°C(MeOH); m/z(%): 284(M^+,68), 269(100); ^{1}H-NMR δ: 1.77(3H,d,J=1Hz,=C$\underline{Me_2}$), 1.97(3H,d,J=1Hz, =C$\underline{Me_2}$), 3.74(3H,s,OMe), 5.35(1H,d like,J=9.5Hz,-$\underline{CH}$=CMe$_2$), 5.91(1H,d,J=9.5Hz,H-1)].

Conformational analysis of the obtained carbamates (6a,b,c) was made by use of ^{13}C-NMR spectra as follows. The non-substituted carbamate (11) was prepared from 3,4-dihydro-β-carboline (10) with $NaBH_4$-$ClCO_2Me$ in dry THF at -70°C[11: 61%; mp 190-192°C(MeOH); m/z(%): 230(M^+,78), 143(100); ^{1}H-NMR δ: 2.80(2H,t like, J=5.5Hz,H-4), 3.76(3H,s,OMe), 3.80(2H,t,J=5.5Hz,H-3), 4.66(2H,br s,H-1)].

The signals of C-3 in carbamates (6a,b,c) were observed in upfield position [2.3-3.3 ppm(Table)] compared with that of the carbamate (11). This effect can be ascribed to the γ-*gauche* effect of C-1 substituents and so the substituents were proved to be axially oriented.

Treatment of the carbamate (6b) with Zn in AcOH at room temperature gave the amine (7b)[56%; mp 158-159°C(benzene); m/z(%): 226(M^+,100); ^{1}H-NMR δ:1.82(3H,d, J=1Hz,=C$\underline{Me_2}$), 1.88(3H,d,J=1Hz,=C$\underline{Me_2}$), 4.84(1H,d like,J=9Hz,H-1), 5.28(1H,d like, J=9Hz,-$\underline{CH}$=CMe$_2$)].

Reduction of the carbamate (6c) with $LiAlH_4$ in dry THF at room temperature for 5 h gave borrerine (8) [88%; mp 102-103°C(haxane); m/z(%): 240(M^+,42), 197(69), 182(100); ^{1}H-NMR δ: 1.86(3H,d,J=1.3Hz,=C<u>Me</u>$_2$), 1.88(3H,d,J=1.3Hz,=C<u>Me</u>$_2$), 2.43(3H, s,N-Me), 4.07(1H,d like,J=9.5Hz,H-1), 5.21(1H,d like,J=9.5Hz,-C<u>H</u>=CMe$_2$); ^{13}C-NMR δ: 18.5(q), 21.6(t), 26.1(q), 43.3(q), 53.2(t), 59.9(d), 108.0(s), 110.7(d), 118.2(d), 119.3(d), 121.3(d), 124.5(d), 127.6(s), 134.4(s), 136.1(s), 137.3(s)]. ^{1}H- and ^{13}C-NMR spectra of the synthetic compound (8) were identical with those of the natural alkaloid, borrerine.[9]

Application of the present method to tryptophan derivatives is in progress.

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8) Satisfactory spectral data and elemental analyses were obtained for all new compounds. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ at 270 MHz and 67.8 MHz, respectively with Me_4Si as an internal standard. ^{1}H- and ^{13}C-NMR spectra of the carbamates (<u>6a,b,c</u> and <u>11</u>) were run at 50°C.

9) Prof. M. Koch, private communication. ^{13}C-NMR data of our synthetic compound was identical with that from Ph.D. thesis of F. Tillequin within ±0.1 ppm.

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