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Synthesis of Vinca Alkaloids and Related Compounds LXXXIII[1]. Unexpected Pictet-Spengler Side-reaction.

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Abstract: Subjection of tryptamine **1** to the action of aldehyde **2d** a substantial amount of dimeric naphthyridine **5** was formed along with the indolo-quinolizidine derivatives **6a** and **6b**.

In the initial stage of the synthesis of the eburnane-type alkaloids (e.g. vincamine) the condensation reaction of tryptamine (**1**) either with dicarboxylic acid aldehyde **2a** , or with diester aldehyde **2c** has frequently been used. As a result of this Pictet-Spengler-type reaction, followed by ring-forming internal acylation, the desired pentacyclic (**3**) or tetracyclic (**4**) products were obtained in good yields[2].

We should like to disclose our observation concerning an unexpected variation of this reaction. If instead of **2a** or **2c** the half-ester of the corresponding acid **2d**[3] was used, under the same reaction conditions the dimeric product, naphthyridine derivative **5**[4] was isolated in 24% yield, in addition to 26,9 % of the two additional isomeric tryptamides (**6a**[5] 20,2 % , **6b**[6] 6,7 %). The new reagent **2d**[3] was prepared by partial hydrolysis of **2c**[7]. The stereostructure of **5** was proved by NOE measurements.

The Pictet-Spengler reaction has long been an important procedure for the synthesis of both indole and isoquinoline alkaloids[8], and surprisingly few side-reactions have been reported. To rationalize the formation of the dimer in substantial amount in this case we may assume that the imine intermediate is protonated internally by the carboxylic acid function (see **7**) thus causing some steric hindrance for the ring closure. At the same time the nucleophilic amino group of a second tryptamine is easily available, and the junction of the two amines is followed by an internal acylation.

We assume that this type of side reaction (i.e. coupling of two amines) may occur in almost all Pictet-Spengler reaction. The aminal is formed in some extent equilibrating with the Schiff base, and if some stabilizing factors, e.g. internal acylation in this case, prevail, one can isolate the compounds derived from this intermediate. Another interesting example, entirely different from the above described, will be reported soon.

ACKNOWLEDGEMENT

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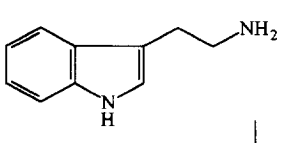

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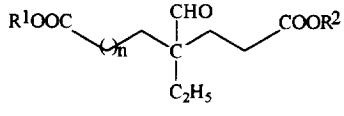

2

	R^1	R^2	n
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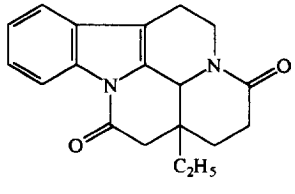
b	H	H	1
c	CH_3	CH_3	1
d	H	CH_3	1



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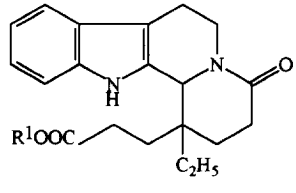

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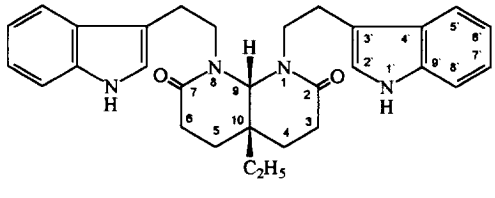

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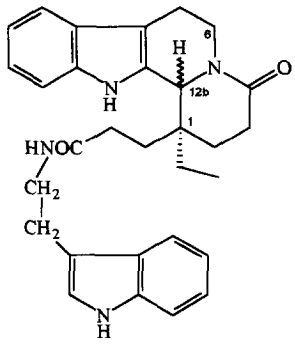

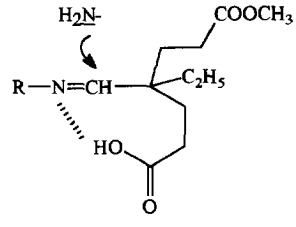

7

6a 12b-H, 1-Et cis

6b 12b-H, 1-Et trans

REFERENCES AND NOTES

1. For part LXXXII see Moldvai, I.; Szántay Jr, Cs.; Szántay, Cs. *Heterocycles, in press.*

2. Saxton, J.E. in *"Indoles"* Part Four Ed. by J.E. Saxton. J. Wiley and Sons, New-York, 1983; pp. 439-465.

3. **2d**: (64%); bp. 185-190°C/0.2 mm; MS m/z (%): 230(M^+, 3.7, $C_{11}H_{18}O_5$), 143(87); ^{1}H NMR($CDCl_3$): 0.85(3H, t, CH_3), 3.65(3H, s, CO_2CH_3), 9.38(1H, s, CHO).

4. **5**: mp. 224°C(CH_3CN); IR(KBr): 3260(indole NH), 1620 cm^{-1} (lactam CO); MS m/z (%): 482(M^+, 12.5, $C_{30}H_{34}N_4O_2$), 339(8.5), 143(100); ^{1}H NMR(400 MHz, $CDCl_3$+d_6-DMSO): 0.72(3H, t), 1.29(2H, q), 1.55 (2H, td, 4-H"$_{ax}$"+ 5-H"$_{ax}$"), 1.72(2H, td, 4-H"$_{eq}$"+5-H"$_{eq}$"), 2.45(4H, t, 3`-$CH_2$), 2.95(4H, t, N-$CH_2$), 3.15(2H, m, 3-H"$_{ax}$"+ 6-H"$_{ax}$"), 4.03 (2H, m, 3-H"$_{eq}$"+6-H"$_{eq}$"), 4.32(1H, s, 9-H), 6.9(2H, d, J=2 Hz, 2`-H), 7.02(2H, td, 6`-H), 7.12(2H, 7`-H), 7.34(2H, dd, 8`-H), 7.62(2H, dd, 5`-H), 9.75(2H, s, NH); ^{13}C NMR 7.45(CH_3), 23.72(3`-$CH_2$), 27.43(4-C), 29.45(3-C), 31.52(Et-$CH_2$), 36.47(10-C), 47.44($NCH_2$), 78.81(9-C), 111.59(8`-C), 111.59(3`-C), 118.59(5`-C), 118.59(6`-C), 121.25(2`-C), 122.54(7`-C), 127.37(4`-C), 136.51(9`-C), 170.83(CO).

5. **6a**: mp. 245°C(CH_3CN); IR(KBr): 3350, 3250(amide and indole NH), 1650(amideCO), 1618 cm^{-1}(lactam CO); MS m/z (%): 482(M^+, 54.7, $C_{30}H_{34}N_4O_2$), 171(100); ^1H NMR($CDCl_3$+d_6-DMSO): 1.05 (3H, t, CH_3), 3.36(2H, q, after D_2O exchange t, NH-CH_2-CH_2), 4.76(1H, s, 12b-H), 5.0(1H, m, 6-H_{eq}), 6.85-7.5(9H, m, aromatic), 9.75(2H, s, indole NH).

6. **6b**: mp. 161°C(CH_3OH); IR(KBr): 3400(indole NH), 1610, 1560 cm^{-1} (amide and lactam CO); MS m/z (%): 482(M^+, 44.9, $C_{30}H_{34}N_4O_2$), 481(100), 171(51.8); ^1H NMR($CDCl_3$+d_6-DMSO): 0.76 (3H, t, CH_3), 3.60(2H, q, after D_2O exchange t, NH-CH_2-CH_2), 4.88(1H, s, 12b-H), 5.12(1H, m, 6-H_{eq}), 7.00-7.65(9H, m, aromatic), 10.59 and11.62(2H, s, indole NH).

7. Kuehne, M.E. *J. Amer. Chem. Soc.* **1964** , 86 , 2946.

8. Cox, E.D. and Cook, J.M. *Chem. Rev.* **1995,** 1797, and citations therein.

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