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SYNTHESIS OF 2-(DIMETHYLALLYL)-N-HYDROXYTRYPTOPHANS FROM INDOLE

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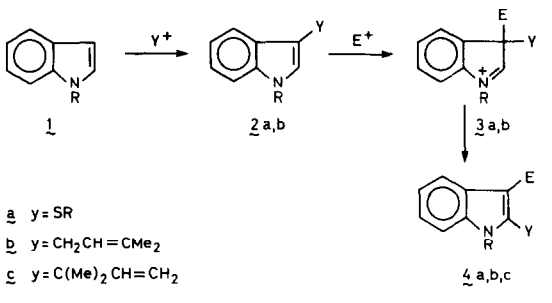
Abstract: A mild and general method for the synthesis of dimethylallyl tryptophan derivatives **11** and **12** is described. Reaction of the 3-(γ,γ-dimethyl-allyl) indoles **7a** or **7b** with the nitroso olefin **8** yields the cycloadducts **9a** (93%) and **9b** (87%), respectively. Subsequent treatment of **9a** with trifluoroacetic acid affords the 2-(dimethylallyl) tryptophan derivatives **11a** and **12a** in a 9:1 ratio (97% yield). Isomerisation of **9b** gave only **11b** (88% yield).

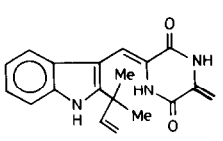
We have recently described a general method for the preparation of 2-(alkylthio) tryptophans and the corresponding N-hydroxy derivatives from indoles[1]. The concept used is based on the reaction of indoles having an alkylthio substituent at C(3), *e.g.* **2a**, with an electrophile, *viz.* a nitroso olefin derivative (Scheme I). This reaction yields **4a** in which the alkylthio group has migrated from C(3) to C(2)[2]. This approach has been examplified[3] by a synthesis of tryptathionine, the characteristic structural element of toxic principles of members of the mushroom Amanita Phalloides[4].
Subsequently we became intrigued by the potential usefulness of this scheme for the synthesis of 2-(dimethylallyl)-indole derivatives **4b-c**.

scheme I

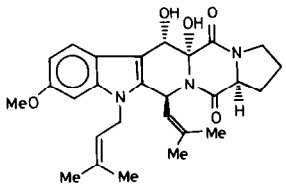


Several mould metabolites have been isolated featuring a dimethylallyl moiety at C(2) of a tryptophan system. Examples having an α,α-dimethylallyl or an γ,γ-dimethylallyl moiety are Neoechinulin B (5)[5] and Fumitremorgin B (6)[6].

Figure



5



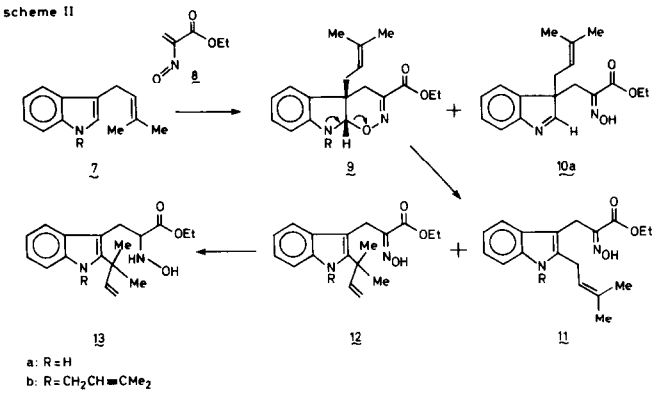
6

Various attempts to synthesize indole alkaloids featuring one of these dimethylallyl moieties at the C(2) position of tryptophan have been made made[7]. Most satisfactory is the prenylation of tryptophan derivatives[8], which has been used in a biomimetic approach to 6. However, no approach starting from indole (1) has been reported. Such an approach seemed attractive to us as it might allow facile introduction of substituents in the indole nucleus prior to the introduction of the amino acid side chain and the dimethylallyl moiety. Several of the above mentioned alkaloids *e.g.* 6 have such a substituent in the indole nucleus.

The purpose of this letter is to show that the 2-(dimethylallyl)-indoles **4b,c** can be prepared indeed from **2b** as depicted schematically in Scheme I. The indoles prepared have as an additional feature the presence of an N-hydroxy-α-amino acid side chain at C(3), which renders these compounds into versatile synthons[9].

Treatment of **7a** - prepared according to Casnati *et.al.*[10] - with the nitroso olefin **8** - prepared *in situ*[9] from ethyl α-(hydroxyimino)-β-bromopropanoate (1.1 equiv., dichloromethane, 24 h, 20 °C, argon atmosphere) - gave a 2:1 mixture of the cycloadduct **9a**[11] and its ring-opened isomer **10a**[12] in 93% overall yield (Scheme II).

scheme II



a: R=H
b: R=$CH_2CH{=}CMe_2$

Separation of the isomers could be achieved by flash column chromatography (Silicagel 60, dichloromethane/n-hexane, 1/1, v/v). When **7b**[13] was subjected to these reaction conditions only cycloadduct **9b**[14] was formed (87% yield). Subsequently, isomerisation was achieved using trifluoroacetic acid (5 equiv., dichloromethane, 1 h, 20 °C). Compound

9a gave the compounds **11a**[15] and **12a**[16] in a 9:1 ratio (97% overall yield). These two isomers could be separated by crystallisation (dichloromethane/n-hexane). The same result was obtained when a mixture of **9a** and **10a** was used. Isomerisation of **9b** afforded **11b**[17] (88% yield); in this case **12b** could not be detected.

The formation of **11** and **12** can be rationalized as follows. The protonated form of **9** is in equilibrium with its ring-opened tautomer, an indoleninium derivative. The latter species might undergo either an C(3)-C(2) allyl shift followed by rearomatization to afford **11** or a Cope-like rearrangement to give **12** subsequent to rearomatisation.

Finally, the oximino group of **12a** was reduced selectively to an N-hydroxyamino function to afford **13a**[18] (79% yield, trimethylamine borane and HCl in ethanol[9]).

We are currently applying **11a** and **13a** in projected syntheses of indole alkaloids. One such study describes the synthesis of **5**.

REFERENCES

1. Plate, R.; Ottenheijm, H.C.J.; Nivard, R.J.F. *J.Org.Chem.* **1984**, *49*, 540.
2. The same rearrangement is obtained when a strong acid (trifluoroacetic acid) is used as electrophile instead of the nitrosoolefin. This reaction affords 2-alkylthioindoles **4a** (E=H) in high yield; Plate, R.; Ottenheijm, H.C.J. manuscript submitted.
3. Plate, R.; Nivard, R.J.F.; Ottenheijm, H.C.J. manuscript submitted
4. For recent reviews see: Wieland, Th. *J. Peptide Protein Res.* **1983**, *22*, 257; Wieland, Th.; Faulstich, H. *Plant and Fungal Toxins, Handbook of Natural Toxins* 1; Keeler, R.F.; Tu, A.T.; Eds., M. Dekker, New York, 1983, p. 585.
5. Marchelli, R.; Dossena, A.; Pochini, A.; Dradi, E. *J. Chem. Soc. Perkin Trans I*, **1977**, 713.
6. Yamazaki, M.; Fujimoto, H.; Akiyama, T.; Sankawa, U.; Iitaka, Y. *Tetrahedron Lett.* **1975**, 27.
7. Jackson, A.H.; Smith. A.E. *Tetrahedron* **1965**, *21*, 989. Casnati, C.; Marcelli, R.; Pochini, A. *J. Chem. Soc. Perkin Trans.I* **1974**, 754. Inada, S.; Nagai, K.; Takayangi, Y.; Okazaki, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 833. Sammes, P.G.; Weedon, A.C. *J. Chem. Soc. Perkin Trans I* **1979**, 3054.
8. Nakagawa, M.; Matsuki, K.; Hasumi, K.; Taniguchi, M.; Hino, T. *Heterocycles* **1982**, *19*, 156. Nakagawa, M.; Matsuki, K.; Hino, T. *Tetrahedron Lett.* **1983**, *24*, 2171.
9. Ottenheijm, H.C.J.; Plate, R.; Noordik, J.H., Herscheid, J.D.M. *J. Org. Chem.* **1982**, *47*, 2147.
10. Casnati, G.; Francioni, M.; Guareshi, A.; Pochini, A. *Tetrahedron Lett.* **1969**, 2485.
11. **Compound 9a** (oil): EIMS: exact mass calcd. for $C_{18}H_{22}N_2O_3$ $[M]^+$ 314.1630, found m/e 314.1634. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=7.14-6.46 (m, 4H, indoline C(4)-C(7)H), 5.32 (s, 1H, indoline C(2)H), 5.14 (m, 1H, C=CH), 4.90 (s(br), 1H, indoline NH), 4.25 (q, 2H, OCH_2CH_3), 3.00 and 2.70 (AB spectrum, $^2J_{AB}$=15.8 Hz, 2H, indoline C(3)CH_2),

2.40 (d, ^3J=7.6 Hz, 2H, indoline C(3)-CH_2-CH=), 1.72 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.29 (t, 3H, OCH_2CH_3).

12. **Compound 10a** (oil): EIMS: exact mass calcd. for $C_{18}H_{22}N_2O_3$ $[M]^+$ 314.1630, found m/e 314.1620. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=7.1-6.4 (m, 4H, indolenine C(4)-C(7)H), 5.5 (s, 1H, indolenine C(2)H), 5.1 (m, 1H, C=CH), 4.20 (dq, 2H, OCH_2CH_3), 3.1 and 2.5 (AB spectrum, $^2J_{AB}$=15 Hz, 2H, indolenine C(3)CH_2), 2.4 (d, ^3J=7.5 Hz, 2H, indolenine C(3)-CH_2-CH=), 1.7 (s, 3H, CH_3), 1.5 (s, 3H, CH_3), 1.3 (t, 3H, OCH_2CH_3).
13. Bocci, V.; Casnati, G.; Dossena, A.; Villani, F. *Synthesis* **1976**, 414.
14. **Compound 9b** (oil): EIMS: exact mass calcd. for $C_{23}H_{30}N_2O_3$ $[M]^+$ 382.2256, found m/e 382.2264. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=7.10-6.30 (m, 4H, indoline C(4)-C(7)H), 5.35-4.90 (m, 2H, 2xC=CH), 5.20 (s, 1H, indoline C(2)H), 4.20 (dq, 2H, OCH_2CH_3), 3.95 (d, ^2J=7 Hz, 2H, N-CH_2), 3.05 and 2.40 (AB spectrum, $^2J_{AB}$=15 Hz, 2H, indolenine C(3)CH_2), 2.35 (d, ^3J=7 Hz, 2H, indoline C(3)-CH_2-CH=), 1.73 (s, 6H, 2xCH_3), 1.65 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.25 (t, 3H, OCH_2CH_3).
15. **Compound 11a**: m.p. 127-129 °C (CH_2Cl_2/n-hexane): CIMS: exact mass calcd. for $C_{18}H_{23}N_2O_3$ $[M+1]^+$ 315.1709, found m/e 351.1712. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=7.80 (s(br), 1H, indole NH), 7.74-7.00 (m, 4H, indole C(4)-C(7)H), 5.32 (m, 2H, C=CH), 4.22 (q, 2H, OCH_2CH_3), 4.04 (s, 2H, indole C(3)-CH_2), 3.60 (d, ^3J=7.3 Hz, 2H, C=CH-CH_2), 1.75 (s, 6H, 2xCH_3), 1.26 (t, 3H, OCH_2CH_3). Anal. calcd. for $C_{18}H_{22}N_2O_3$ (M=314.385) C, 68.77; H, 7.05; N 8.91; found C, 68.71, H 7.06; N 8.88.
16. **Compound 12a**: m.p. 86-88 °C (CH_2Cl_2/n-hexane): CIMS: exact mass calcd. for $C_{18}H_{23}N_2O_3$ $[M+1]^+$ 315.1709, found m/e 315.1715. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=9.20 (s(br), 1H, NOH), 8.90 (s, 1H, indole NH), 7.60-6.90 (m, 4H, indole C(4)-C(7)H), 6.19 (dd, $^3J_{trans}$=17.6 Hz, $^3J_{cis}$=10.5 Hz, 1H, C*H*=CH_2), 5.19 and 5.16 (2xdd, $^3J_{trans}$=17.6 Hz, $^3J_{cis}$=10.5 Hz, $^2J_{gem}$=1.2 Hz, 2H, CH=CH_2), 4.14 (q, 2H, OCH_2CH_3), 1.58 (s, 6H, $C(CH_3)_2$), 1.12 (t, 3H, OCH_2CH_3). Anal. calcd. for $C_{18}H_{22}N_2O_3$•1/6 CH_2Cl_2 (M=328.539) C, 66.42; H, 6.85; N 8.53; found C, 66.50, H 6.88; N 8.55.
12a was found to be identical to a product obtained by an alternative route, see Plate, R.; Ottenheijm, H.C.J. manuscript submitted.
17. **Compound 11b**: m.p. 138-142 °C (CH_2Cl_2/n-hexane): EIMS: exact mass calcd. for $C_{23}H_{30}N_2O_3$ $[M]^+$ 382.2256, found m/e 382.2264. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=8.50 (s(br), 1H, indole NOH), 7.72-6.87 (m, 4H, indole C(4)-C(7)H), 5.40 (m, 2H, 2xC=CH), 4.60 (d, ^3J=7 Hz, 2H, N-CH_2-CH=), 4.17 (q, 2H, OCH_2CH_3), 4.03 (s, 2H, indole C(3)-CH_2), 3.56 (d, ^3J=7 Hz, 2H, indole C(2)-CH_2-CH=), 1.92 and 1.77 (2xs, 12H, 4xCH_3), 1.25 (t, 3H, OCH_2CH_3). Anal. calcd. for $C_{23}H_{30}N_2O_3$ (M=382.504) C, 72.22; H, 7.91; N 7.32; found C, 71.90, H 7.90; N 7.22.
18. **Compound 13a**: (foam). EIMS: exact mass calcd. for $C_{18}H_{24}N_2O_3$ $[M]^+$ 316.1787, found m/e 316.1784. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=8.90 (s(br), 1H, indole N'H'), 7.60-7.00 (m, 4H, indole C(4)-C(7)H), 6.14 (dd, $^3J_{trans}$=17.6 Hz, $^3J_{cis}$=10.2 Hz, 1H, CH=CH_2), 5.50 (s(br), 2H, NHOH), 5.28 and 5.13 (2xdd, $^3J_{trans}$=17.6 Hz, $^3J_{cis}$=10.2 Hz, $^2J_{gem}$=1.2 Hz, 2H, CH=CH_2), 4.16 (q, 2H, OCH_2CH_3), 4.02 (X part of ABX spectrum, $^3J_{AX}$=6.3 Hz, $^3J_{BX}$=9.0 Hz, 1H, CH_2-C'H'), 3.21 and 3.12 (AB part of ABX spectrum, $^3J_{AX}$=6.3 Hz, $^3J_{BX}$=9.0 Hz, $^2J_{AB}$=15.3 Hz, 2H, CH_2-CH), 1.56 (s, 6H, $C(CH_3)_2$), 1.18 (t, 3H, OCH_2CH_3).

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