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Synthesis of Canthine/Erythrinane Alkaloid Analogs[1]

Short Communication

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The pentacyclic lactams **9**, **11**, and **14** were prepared using a thermal condensation of tryptamine with symmetrical oxodiesters **3** and **4** as the key step. The formation of the ring E in the tetracyclic compounds **5**, **6**, **8**, **10**, **12**, and **13** is strongly dependent on the ring size.

[Keywords: Pictet-Spengler reaction; Lactams, ring-size effect in the formation of; Indolo(2,3−g)indolizine and (2,3−a)quinolizine derivatives]

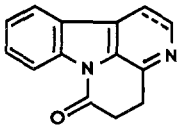
Synthese von Analoga der Canthin/Erythrina Alkaloide
(Kurze Mitteilung)

Die pentacyclischen Verbindungen **9**, **11** und **14** wurden durch thermische Kondensation von Tryptamin mit symmetrischen Oxodiestern **3** und **4** als wichtigster Reaktionsstufe dargestellt. Die Bildung des Ringes E in den tetracyclischen Verbindungen **5**, **6**, **8**, **10**, **12** und **13** ist stark von der Ringgröße abhängig.

Indole alkaloids of the eburnane type have been the subject of considerable synthetic efforts[2] because of their potent pharmacodynamic activity. In the past decade a number of analogs were synthesized including bases with modified skeleton, e.g. those[3] lacking ring D. Recently, we have focused our attention on the chemistry of canthine-like bases[4,5] (**1**). In continuation of our efforts in this field we report here on the synthesis of analogs of canthine/eburnane bases manifesting themselves by the presence of a quaternary carbon atom next to the aromatic system, a structural feature common to the erythrinane alkaloids (**2**).

Dimethyl esters of 4-oxoheptanedioic and 5-oxononanedioic acids (**3**)

and (**4**) were condensed with tryptamine in refluxing xylene to give tetracyclic lactam esters **5** (43%) and **6** (52%), respectively. The former of them was alternatively prepared (55%) by heating tryptamine with hydrochelidonic acid dilactone (**7**) in chlorobenzene or diglyme, followed by refluxing in a mixture of methanol and hydrochloric acid.



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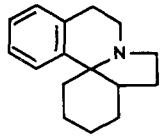
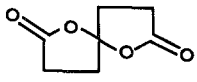


2

$O{:}C(CH_2(CH_2)_nCOOMe)_2$

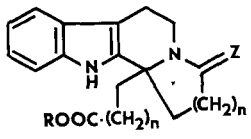
3: n: 1

4: n: 2



7

The ability of the lactam esters to cyclize and yield pentacyclic dilactams with both acidic and basic reagents was shown to be strongly dependent on the size of the ring E to be closed. Thus, in trifluoroacetic acid at r.t., the cyclization of the lactam ester **5** and the corresponding acid[6] **8** to dilactam **9** was completed within 6 days (78%) and 2.5 h (89%), respectively. On the other hand, the lactam ester **6** and the related acid[6] **10** were recovered unchanged under these conditions. Likewise, using sodium hydride (1 eq) in refluxing benzene, the lactam ester **5** was converted to **9** within 2 h (83%), while the reaction of the homolog **6** could not be forced to completion even by 40 h at reflux (3 eqs of NaH) and furnished the dilactam **11** in a low yield (20%).



5: n: 1, R: Me, Z: O

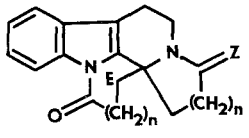
6: n: 2, R: Me, Z: O

8: n: 1, R: H, Z: O

10: n: 2, R: H, Z: O

12: n: 1, R: Me, Z: H_2

13: n: 2, R: Me, Z: H_2



9: n: 1, Z: O

11: n: 2, Z: O

14: n: 1, Z: H_2

The lactam esters **5** and **6** were converted to aminoesters **12** (45%) and **13** (46%) by standard procedures (P_2S_5, pyridine, heat; Raney-Ni, aq. dioxane, heat). Similarly as in the case of lactams, the aminoester **12** cyclized smoothly to give the target base **14** upon exposure to both trifluoroacetic acid r.t. for 5 days (86%) and sodium hydride (1 eq) in

refluxing benzene for 4.5 h (91%). On the other hand all attempts at ring closure in the aminoester **13** failed, illustrating thus further a remarkable ring-size effect in the cyclization step.

Selected data of the new compounds

5: M.p. 178–180.5 °C. ^{1}H-NMR (*DMSO-d_6*): δ 11.07 (1 H, bs), 7.5–6.8 (4 H, m), 4.21 (1 H, bm), 3.55 (3 H, s). IR ($CHCl_3$): 1 725, 1 668 cm^{-1}. MASS m/*z* (%): 312 (6; M^+), 280 (3), 279 (3), 226 (17), 225 (100), 224 (5), 167 (5).

6: M.p. 152–154 °C. ^{1}H-NMR ($CDCl_3$): δ 8.28 (1 H, bs), 7.5–6.9 (4 H, m), 5.05 (1 H, bm), 3.60 (3 H, s). IR ($CHCl_3$): 1 720, 1 630 cm^{-1}. MASS m/*z* (%): 340 (3; M^+), 309 (2), 240 (19), 239 (100), 209 (3), 144 (7).

8: M.p. 245–247 °C (dec.). ^{1}H-NMR (*DMSO-d_6*): δ 11.00 (1 H, bs), 7.4–6.8 (4 H, m), 4.20 (1 H, bm). IR (nujol): 1 700, 1 650 cm^{-1}. MASS m/*z* (%): 290 (7; M^+), 226 (18), 225 (100), 224 (6), 167 (4).

9: M.p. 160.5–162 °C. ^{1}H-NMR ($CDCl_3$): δ 8.15 (1 H, m), 7.5–7.1 (3 H, m), 4.45 (1 H, bm). IR (nujol): 1 680, 1 630 cm^{-1}. MASS m/*z* (%): 281 (19), 280 (100; M^+), 279 (94), 225 (15), 224 (48), 167 (29).

10: M.p. 239.5–242.5 °C (dec.). ^{1}H-NMR (*DMSO-d_6*): δ 10.80 (1 H, bs), 7.4–6.8 (4 H, m), 4.80 (1 H, bm). IR (nujol): 1 700, 1 630 cm^{-1}. MASS m/*z* (%): 326 (3; M^+), 240 (20), 239 (100), 144 (5).

11: M.p. 192.5–193.5 °C. ^{1}H-NMR (*DMSO-d_6*): δ 8.50 (1 H, m), 7.5–7.1 (3 H, m), 4.80 (1 H, bm). IR (nujol): 1 680, 1 630 cm^{-1}. MASS m/*z* (%): 309 (20), 308 (99; M^+), 307 (30), 280 (18), 279 (17), 239 (35), 238 (100), 210 (26), 209 (29).

12: M.p. 129.5–130.5 °C. ^{1}H-NMR ($CDCl_3$): δ 8.00 (1 H, bs), 7.40 (1 H, m), 7.2–7.0 (3 H, m), 3.61 (3 H, s). IR ($CHCl_3$): 1 720 cm^{-1}. MASS m/*z* (%): 298 (2; M^+), 267 (2), 212 (18), 211 (100), 210 (6), 167 (4), 154 (2).

13: Glass. ^{1}H-NMR ($CDCl_3$): δ 7.95 (1 H, bs), 7.5–7.0 (4 H, m), 3.60 (3 H, s). IR ($CHCl_3$): 1 720 cm^{-1}. MASS m/*z* (%): 326 (2; M^+), 295 (2), 226 (18), 225 (100), 224 (6), 167 (4).

14: Glass. ^{1}H-NMR ($CDCl_3$): δ 8.23 (1 H, m), 7.35–7.20 (3 H, m). IR ($CHCl_3$): 1 690, 1 620 cm^{-1}. MASS m/*z* (%): 226 (80; M^+), 265 (100), 238 (26), 224 (21), 223 (19), 167 (26).

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[6] Prepared by alkaline hydrolysis of the corresponding lactam esters (70–73%).

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