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REACTIONS WITH INDOLE DERIVATIVES—XLIX[1]

PSEUDOYOHIMBANES FROM METHYLENE LACTAMS

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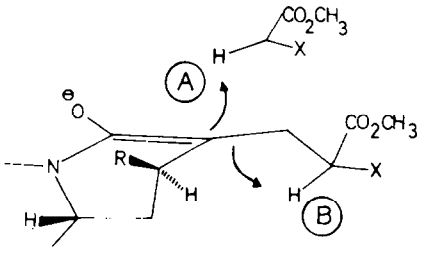
Abstract—The Michael addition of 1,3-dithiane derivatives to methylene lactams is a highly stereoselective process giving rise to very good yields of pseudoyohimbanes. Some useful reactions of the addition products are reported.

In a recent paper[2] we described the preparation and some characteristic transformations of the readily accessible methylene lactams of type **1**. Produced in quantity they are excellent starting materials for natural product synthesis. Especially Michael additions to the exocyclic double bond proved to be useful reactions.[3-5] The stereochemistry of Michael additions with malonic ester derivatives in aprotic polar solvents proved these reactions to be non stereoselective,[6] the stereoisomers **2a** and **2b** being formed in varying amounts depending on structural details in the Michael donor.

Although products of the pseudoyohimbane type **2a** in most cases represent the main reaction product, tedious separation provided pure stereoisomers. This result certainly is connected with the low acidity of α-lactam protons which, after formation of enolate **3**, should quickly give rise to intermolecular (**A**) as well as intramolecular transprotonation processes which, in the intramolecular case (**B**), should also give rise to products of type **2b**.



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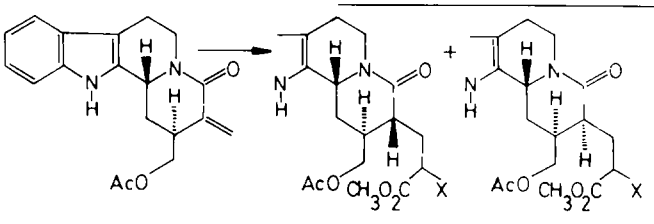
4b, however, in this case a small amount of the stereoisomer was noticed. The configuration **5** was proved by Raney nickel reduction to the known lactam **6** as well as by deuteride reduction and acetylation to indoloquinolizidine **7**, which according to expectation was shown to be a *cis*-quinolizidine (IR- and NMR-data!).[7,8]

As this stereochemical result was independent of



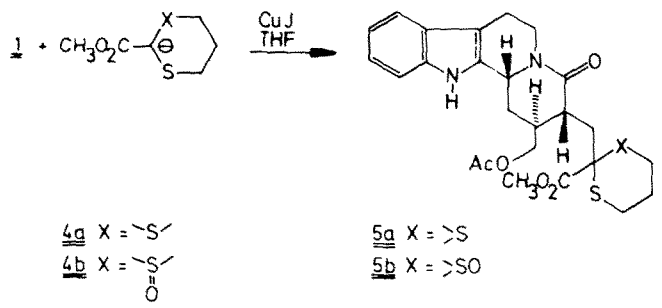
1 **2a** X = CO_2CH_3 **2b** X = CO_2CH_3

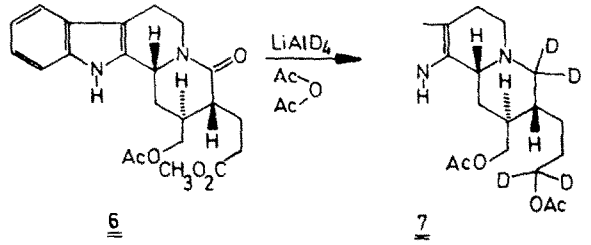
The speculation that in particular the bulky Michael donors, owing to directing effects of the substituent R (α-attack) and hindered rotation as well as hindered intermolecular protonation, should give rise to increasing amounts of **2b** is born out by experiments in the case of t-butyl-malonate.[6] A simple test, showing the influence of intramolecular transprotonation of type **(B)**, should be the addition of Michael donors with no extra proton avialable. For example, 1,3-dithiane derived anions of type **4**, which in several cases proved to be good nucleophiles for 1,4 addition, gave rise to very good yields of only one pure stereoisomer, as in the case of **4a**.

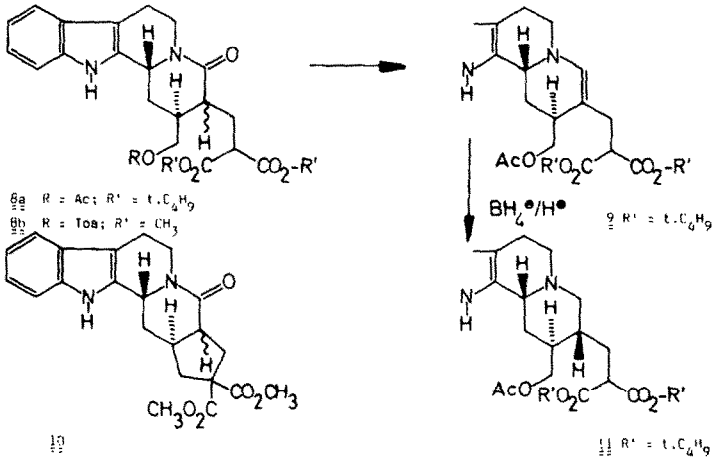
A similar result was observed with monosulfoxide

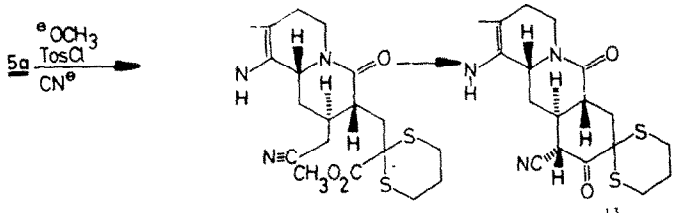
work up procedures and on the mode of protonation as well as the protonating species, **5a** very probably represents the kinetic controlled product of enolate protonation. As a good model for this protonation process the enamine **9**, which can be obtained on low temperature DIBAH reduction of lactam **8a**, was chosen. Borohydride reduction under acid conditions also gave rise to the pseudo-yohimbine configuration exclusively. As the first step in this reduction certainly is protonation of the enamine, this result parallels the outcome of enolate protonation.

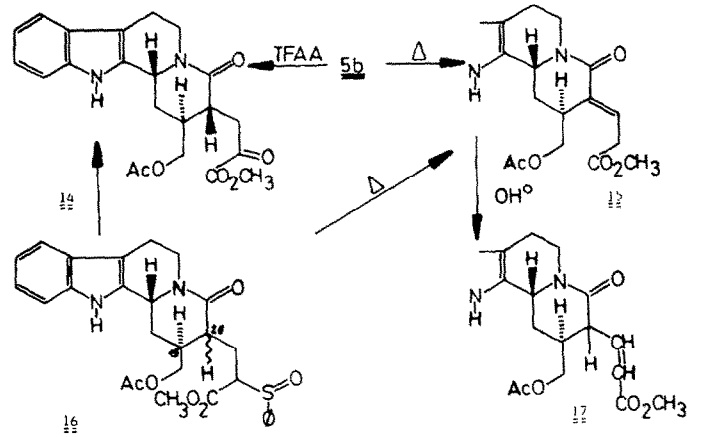
As **9** as well as **11**, may be obtained from both stereosiomers of starting material **8**, this reaction additionally represents a stereoconvergent trans-

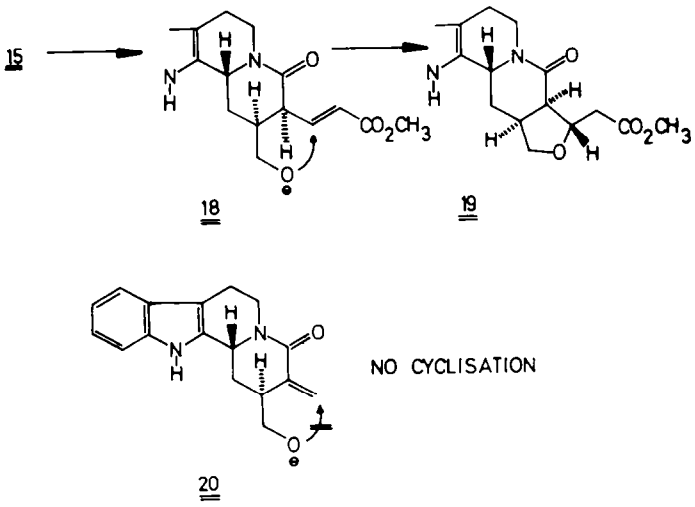

1
CuJ
THF
4a X = S
4b X = SO
5a X = >S
5b X = >SO


LiAlD4
Ac2O
6
7


8a R = Ac; R' = t.C4H9
8b R = Tos; R' = CH3
BH4⊖/H⊕
9 R' = t.C4H9
10
11 R' = t.C4H9


5a
TosCl
CN⊖
12
13


TFAA
5b
Δ
14
16
OH⊖
17



formation of malonate addition products **2a** and **2b**, thus rendering this process highly stereoselective. There is however one substantial advantage for dithiane adducts of type **5**, particularly in nucleophilic displacement reactions. All attempts to displace the oxygen function in **8b** by a cyanide anion led exclusively to cyclisation product **10**, the cyanide anion operating as a proton acceptor rather than as a nucleophile.[6] As no acidic protons are available in **5a** and **5b**, normal substitution reactions were anticipated for these intermediates. This unfortunately, was not the case with monosulfoxide **5b**. Although formation of the tosylate proceeded without difficulty, cyanide displacement met with failure. This probably is due to the close proximity of the nucleophilic sulfoxide group to the reaction centre. In line with this explanation the simple dithiane **5a**, lacking this intervening group, is easily transformed to nitrile **12** by tosylation and cyanide anion displacement.

Treatment of ester nitrile **12** with potassium-t-butoxide in DMSO smoothly generates the pentacyclic intermediate **13** bearing interesting functionality in various positions.

Although sulfoxide **5b** created problems in the substitution reaction, two transformations of this intermediate are noteworthy. According to expectation **5b**, under Pummerer conditions, was easily transformed into the α-ketoester **14**, and the same pure stereoisomer was also formed in good yield from mixtures of stereoisomers of ester sulfoxide **16**, which was prepared from methylene lactam **1** under usual Michael addition conditions. Clearly epimerisation at C-20 is possible at the Pummerer stage and this may be explained by protonation of the amide group and additional enolisation of the α-ketoester.

A quite unexpected result was obtained under thermal conditions. Heating in dioxane resulted in the formation of the unsaturated lactam **15** (*E*/*Z* mixture), the *E*-configuration as indicated in the formula representing the main reaction product.

Interestingly, the same unsaturated compound was obtained from sulfoxide **16**. A mechanistic discussion of this behaviour is postponed till more experimental results are available, particularly regarding whether the lactam group is involved in the process. In both cases none of the corresponding unsaturated ester **17** could be detected either spectroscopically or by TLC, thus indicating **15** to be the more stable isomer. The possibility for equilibration is proved by methanolysis of the acetate group. Under these conditions, starting with **15**, the formation of the tetrahydrofuran derivative **19** was observed. According to Baldwin's rules[9] this intramolecular Michael addition is only possible in **18** (exo-process).

To prove this, several attempts were made to cyclize the unsaturated lactam **20** under basic conditions, but no tetrahydrofuran was formed.

EXPERIMENTAL

Addition of 2-methoxycarbonyl-1,3-dithiane **4a**. 550 mg dithiane **4** was dissolved in 40 ml dry THF and −70° was treated with 1.6 ml of a 1.6 M BuLi soln. After 1 hr at −70°, 295 mg CuI was added. After another hr, 500 mg of **1** dissolved in 10 ml dry THF was added and the temp allowed to rise to −10°. The process was monitored by TLC and after disappearance of the starting material the soln was poured into ice-cold 0.4 M citric-acid soln and extracted with CH_2Cl_2. The extract was washed with brine dried over $MgSO_4$ and evaporated *in vacuo*. After filtration over silica, 686 mg (88%) of adduct **5a** was obtained, m.p. 157° (dec) after crystallisation from acetone. UV (MeOH): Indole absorption (qualitative); IR (KBr): 3400, 1740, 1730, 1625 and 745 cm^{-1}; NMR ($CDCl_3$): δ 8.4 [1], 6.95-7.60 [4] m, 5.1 [1] dd, J = 8.5 Hz, J = 2.5 Hz, 4.85 [1] dd, J = 11 Hz, J = 4.5 Hz, 4.0 4.4 [2] m, 3.73 [3] s, 2.1 [3] s; MS (210°): *m/e* 502 (M^+, 92%), 468 (18), 443 (40), 396 (27), 325 (82), 251 (20), 237 (100), 184 (39), 169 (40); $C_{25}H_{30}N_2O_5S_2$, Calc: 502.1596; Found: 502.1591.

Addition of monosulfoxide **4b**. 500 mg of **1** was dissolved in 15 ml DMF and 1.3 g of **4b** was added. After addition of 500 mg t-BuOK the mixture was left at room temp for 48 hr. After work up 552 mg (69%) of adduct **5b** was obtained. UV (MeOH): Indole absorption (qualitative); IR (KBr): 3270, 1735, 1625, 1050, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.85 8.85 [1] broad s, 6.95–7.55 [4] m, 4.6–5.1 [2] m, 4.0–4.4 [2] m, 3.74 [3] s, 2.1 [3] s.

For further characterisation, **5b** as well as **5a** were reduced with Raney-Ni to yield the known lactam **6**.

Indoloquinolizidine **7**. 300 mg of **6** dissolved in 15 ml of dry THF was treated with 500 mg of $LiAlD_4$. After work up, the mixture was treated with 20 ml Ac_2O and 10 ml pyridine. After 10 hr at room temp the mixture was evaporated and the residue separated by TLC. 176 mg (58%) of the deuterated compound was isolated. UV (MeOH): Indole absorption (qualitative); IR ($CHCl_3$): 3700, 2100, 1730 cm^{-1};

NMR ($CDCl_3$): δ 8.41 [1] s broad, 6.95–7.55 [4] m, 4.15 [2] d, J = 6 Hz, 4.06 [1] s broad, 2.1 [3] s, 2.01 [3] s; MS (150°): *m/e* 402 (M^+, 100%), 359 (6), 344 (12), 330 (14), 300 (8), 288 (5), 186 (6), 170 (18); $C_{23}D_4H_{26}N_2O_4$. Calc: 402.2457, Found: 402.2456.

Enamine **9**. 420 mg of **8a** was dissolved in 15 ml of dry THF and at −78°, 2 ml of a 1.2 M soln of diisobutyl aluminumhydride was added. After 20 min the mixture was hydrolysed (KOH), filtered and evaporated. After chromatography (silica) 240 mg (57%) of white crystals were obtained. M.p. 138°; UV (MeOH): Indole absorption (qualitative); IR (KBr): 3460, 1725, 1450 cm^{-1}; NMR ($CDCl_3$): δ 7.9 [1] s broad, 7.0–7.5 [4] m, 6.02 [1] s, 4.11 [3] m, 2.13 [3] s, 1.39 [9] s, 1.43 [9] s; MS (150°): *m/e* 524 (M^+, 29%), 522 (83), 450 (27), 309 (100), 206 (22), 223 (43), 184 (9), 169 (13); $C_{30}H_{40}O_6N_2$ Calc: 524.2916, Found: 524.2915.

[2*β* - (*Acetoxymethyl*) - 1,2,3,4,6,7,12,12*β* - *octahydroindolo*[2,3 - *a*]*chinolizin* - 3*α* - *ylmethyl*]*di* - *t* - *butylmalonate* (**11**). 100 mg of **9** was dissolved in 15 ml AcOH and 15 mg $NaBH_4$ was added at 0°. After 10 min the mixture was poured into sat Na_2CO_3aq and extracted with CH_2Cl_2. After evaporation of the solvent the residue was separated by TLC and 47 mg (46%) of **11** isolated. UV (MeOH): Indole absorption (qualitative); IR (KBr): 3400, 2760, 2810, 1725 cm^{-1}, NMR ($CDCl_3$): δ 7.89 [1] s broad, 7.0–7.5 [4] m, 4.19 [2] d, J = 5.5 Hz, 3.9 [1] tr, J = 5 Hz, 2.10 [3] s, 1.44 [9] s, 1.45 [9] s; MS (150°): *m/e* 526 (M^+, 100%), 471 (27), 454 (44), 413 (44), 369 (72), 269 (14), 238 (16), 237 (16), 211 (19), 184 (84), 169 (29); $C_{30}H_{42}O_6N_2$ Calc: 526.3074, Found: 526.3071.

Nitrile **12**. 500 mg **5a** was treated with 20 ml NaOMe soln (2%) for 10 min at room temp, diluted with water, extracted with CH_2Cl_2 and evaporated. The residue was dissolved in 5 ml pyridine, 1 g of *p*-toluenesulfonic acid chloride was added and this mixture left at room temp for 4 hr. The crude material obtained after usual work up was dissolved in 10 ml DMSO and treated with 300 mg NaCN. After 24 hr at room temp the mixture was mixed with brine and extracted with CH_2Cl_2. After evaporation and chromatography (silica) 300 mg (57%) of **12** was isolated. UV (MeOH): Indole absorption (qualitative); IR ($CHCl_3$): 3470, 2260, 1730, 1640 cm^{-1}; NMR ($CDCl_3$): δ 8.33 [1] s broad, 7.0–7.6 [4] m, 4.78–5.20 [2] m, 3.78 [3] s; MS (280°): *m/e* 469 (M^+, 100%), 435 (10), 410 (85), 363 (35), 323 (28), 237 (60), 184 (20), 169 (80); $C_{24}H_{27}N_3O_3S_2$ Calc: 469.1494, Found: 469.1493.

Keto-nitrile **13**. 150 mg of **12** in 6 ml dry and oxygen-free DMSO was treated with 50 mg t-BuOK. After 24 hr at room temp, dilute acid was added, and the mixture extracted with CH_2Cl_2 and evaporated. After TLC separation 78 mg (56%) of **13** was isolated as a white foam. UV (MeOH): Indole absorption (qualitative); IR ($CHCl_3$): 3470, 2260, 1725, 1650 cm^{-1}; NMR ($CDCl_3$): δ 8.67 [1] s broad, 6.95–7.60 [4] m, 4.78–5.20 [2] m, 4.56 [1] d, J = 12 Hz; MS (290°): *m/e* 437 (M^+, 14%), 410 (17), 382 (7), 343 (8), 334 (10), 277 (13), 249 (13), 237 (100), 184 (11), 169 (34); $C_{23}H_{23}N_3O_2S_2$ Calc: 437.1232, Found: 437.1231.

α-Ketoester **14**. To 200 mg of **5b** in 30 ml of dry CH_2Cl_2 0.3 ml trifluoroacetic anhydride was added and the mixture stirred at room temp for 15 min. This soln was washed with sat $NaHCO_3$aq and evaporated. The product was purified by TLC and afforded 96 mg (61%) of **14** as a slightly yellow foam. IR (KBr): 3300, 1735, 1625, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.4 [1] s broad, 6.95 7.60 [4] m, 4.83–5.03 [2] m, 4.07 4.20 [2] d, J = 5 Hz, 2.10 [3] s; MS (220°): *m/e* 412 (M^+, 71%), 353 (50), 339 (10), 310 (28), 251 (25), 237 (100), 184 (55), 169 (64); $C_{22}H_{24}N_2O_6$ Calc: 412.1634, Found: 412.1634.

The same compound was obtained from **16** which was prepared under the same reaction conditions as **5b** (see above) in 82% yield as 1:1 mixture of stereoisomers at C_{20}.

Data for sulfoxide **16**. IR (MBr): 3400, 1735, 1635, 1050, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.5–8.7 [1] broad, 6.95–7.7 [9] m, 4.55–5.22 [2] m, 3.8–4.5 [2] m, 3.25–3.85 [3] m, 2.05–2.1 [3] m; MS (200°): *m/e* 396 ($M^+ - 126$, 28%), 365 (8), 323 (15), 264 (22), 256 (14), 218 (46), 184 (14), 169 (25), 110 (100); ($C_{28}H_{30}N_2O_6S$–C_6H_6OS) $C_{22}H_{24}N_2O_5$ Calc: 369.1685, Found: 369.1686.

General procedure for sulfoxide elimination. 0.6 mmol of the corresponding sulfoxide was dissolved in 15 ml dry dioxane and the solution refluxed for 4 hr. The soln was diluted with CH_2Cl_2 and washed with sat $NaHCO_3$aq. After evaporation the residue was separated by TLC to yield pure *E*- and *Z*-isomers.

Isomer **15Z**. 41 mg (17%). IR (KBr): 3400, 1735, 1660, 1615, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.39 [1] s broad, 6.95–7.65 [4] m, 6.22 [1] tr, J = 6.5 Hz, 5.15 [1] m, 4.92 [1] dd, J = 4.5 Hz, J = 11 Hz, 4.1–4.4 [2] m, 3.89 [2] d, J = 6.5 Hz, 3.69 [3] s, 2.1 [3] s; MS (150°): *m/e* 396 (M^+, 100%), 365 (16), 336 (27), 323 (86), 263 (58), 249 (28), 198 (64), 184 (34), 169 (36); $C_{22}H_{24}N_2O_5$. Calc: 396.1685, Found: 396.1682.

Isomer **15E**. 133 mg (57%). IR (KBr): 3400, 1740, 1660, 1600, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.1 [1] s broad, 7.0–7.6 [5] m, 5.1–5.3 [1] m, 5.02 [1] dd, J = 4.5 Hz, J = 12 Hz, 4.05–4.32 [2] m, 3.3 [2] d, J = 6.5 Hz, 2.56 [1] ddd, J = 3.5 Hz, J = 4.5 Hz, J = 14 Hz, 1.85 [1] ddd, J = 4.5 Hz, J = 12 Hz, J = 14 Hz, 2.11 [3] s; MS (160°): *m/e* 396 (M^+, 78%), 336 (9), 323 (100), 262 (65), 250 (50), 206 (100), 184 (55), 169 (55); $C_{22}H_{24}N_2O_5$ Calc. 369.1685, Found: 396.1682.

Cyclisation to tetrahydrofuran derivative **19**. 210 mg of **15** was left for 1 hr at room temp in a 2% NaOMe soln. After dilution with water and extraction with CH_2Cl_2, the solvent was evaporated and the residue separated by TLC to afford 84 mg (45%) of **19**.

IR (KBr). 3400, 1740, 1625, 1170, 745 cm^{-1}; NMR ($CDCl_3$): δ 8.43 [1] s broad, 6.95–7.6 [4] m, 4.75–5.2 [2] m, 3.9–4.5 [2] m, 3.69 [3] s, 3.52–3.85 [1] m; MS (170°): *m/e* 354 (M^+, 100%), 323 (18), 299 (16), 279 (24), 264 (18), 237 (46), 184 (34), 169 (42); $C_{20}H_{22}N_2O_4$ Calc: 354.1580, Found: 354.1577.

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