REACTIONS WITH INDOLE DERIVATIVES, XLV

THE STEREOSELECTIVE TOTAL SYNTHESIS OF AKAGERINE

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Abstract —— A stereoconvergent approach to a pentacyclic dilactame (4) is reported and its conversion into the new indole alkaloid akagerine is described.

In 1975 L. Angenot and collaborators described the isolation and structure elucidation of a new type of indole alkaloid from strychnos usambarensis, the roots of which are being used as arrow poison in Central-Africa[2]. By x-ray structure determination the configuration of this new alkaloid - named akagerine - was proven to be (1). The same compound was isolated by W. Rolfsen and coworkers from Uppsala University a few years later[3].

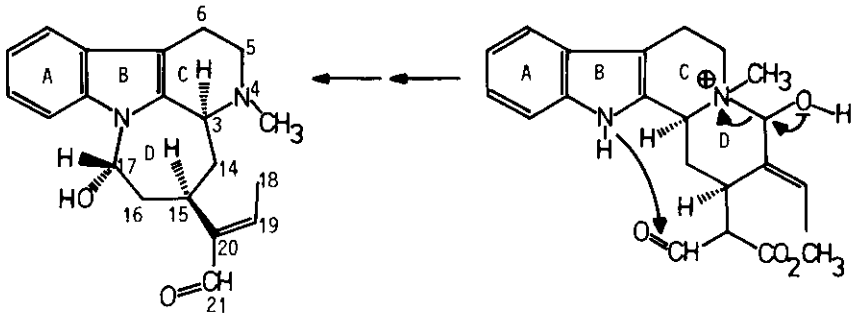
Scheme 1

Biogenetically this compound can easily be linked to dehydro-geissoschizine which recently has been shown to be an important biogenetic intermediate in this field of alkaloids[4]. The methylated aldehyde ammonia of dehydro-geissoschizine (2) could easily open ring D by formation of the unsaturated aldehyde and simultaneously or subsequently ring close to the seven membered ring by nucleophilic attack of N_a to the malonic semi aldehyde moiety.
This particular type of ring closure was planned to be one of the key reactions in the stereoselective total synthesis of akagerine reported in this paper, and it turned out to be a very smooth and efficient process[5]. Starting from acid (3a) the pentacyclic lactame (4) was obtained on treatment with trifluoro-aceticacid-anhydride at room temperature.

Scheme 2

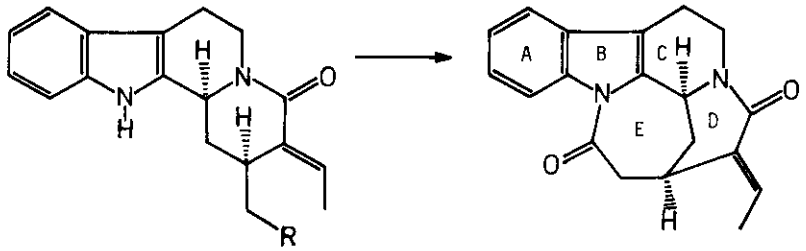
As the same product (E-configuration of the exocyclic double bond) is also obtained from the Z-stereoisomer (5) this cyclisation additionally proves to be a stereoconvergent process giving rise to the "natural" double bond configuration only. A closer inspection of the cyclisation of acid (5) actually did reveal the formation of two lactames after short reaction times (see

Scheme 1



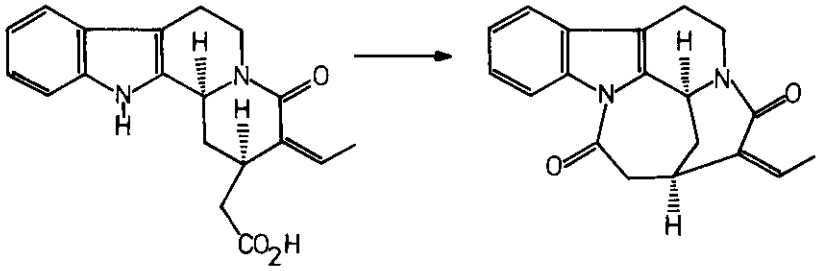
1 2

Scheme 2



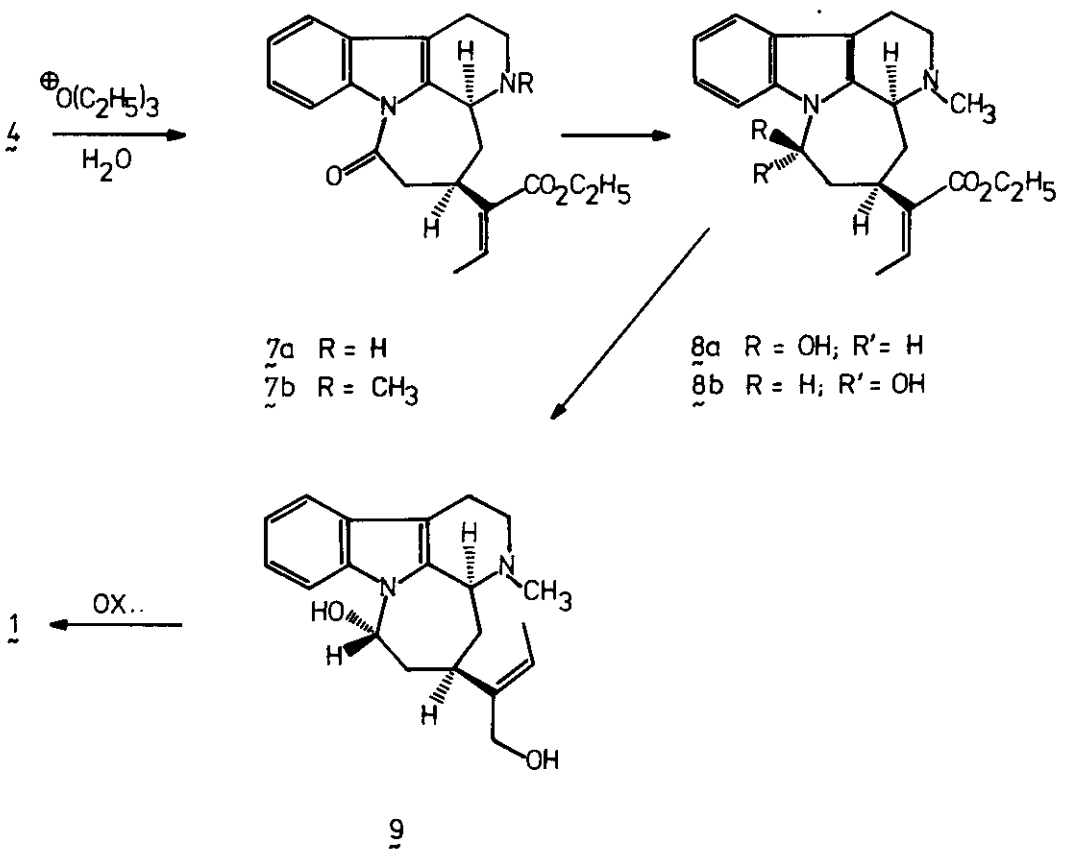
3a R = COOH
3b R = $COOCH_3$
3c R = CH_2OH

4



5 6

Scheme 3



experimental). On separation of this mixture the Z-stereoisomer (6) was isolated indeed, and as (6) on further treatment is cleanly converted into (4) one can safely identify (4) as the product of thermodynamic control in this cyclisation reaction.

For further elaboration of intermediate (4) the selectivity of ring opening reactions had to be checked. As expected nucleophilic attack easily takes place at the C_{17}-carbonyl group, thus giving rise in methanolysis for instance to methylester (3b)[5] - an important intermediate en route to geissoschizine[6,7]. The special reactivity of this C_{17}-carbonyl group can be judged from its smooth reaction even with potassium-tert.butylate to form the corresponding ester[8]. Completely in line with these observations is the result of the hydride reduction of (4). Quick reduction at C_{17} by the triethyl-borohydride anion is accompanied by instantaneous ring opening and reduction of the resulting aldehyde to eventually yield carbinol (3c) in excellent yield. This experiment indicates that reduction of this group, which is necessary for akagerine - synthesis will have to be postponed to a later stage with less strain and ring fission tendency.

To these ends selective ring opening of ring D had to be achieved first, and according to the higher donor capacity of N_b, electrophilic attack was expected to preferentially take place at this carbonyl group.

In fact Meerwein-reagent was shown to alkylate this oxygen atom exclusively giving rise to the corresponding alkoxy iminium salt which on further treatment with water opened ring D to form ester (7a) in a completely stereospecific manner.

Scheme 3

Although selective and stereospecific as easily can be judged from the NMR-data of (7a) (see experimental) this process unfortunately turned out to be very dependant on the quality of the Meerwein-reagent used. Failure in certain cases could not be satisfactorily explained and merits further investigation. Subsequent introduction of the N_b methyl group by the well established reductive amination process[9] is very efficient and high chemical yields are obtained if for prevention of dimerisation reactions a surplus of formaldehyde is used.

Intermediate (7b) then looks very promising for a direct transformation into akagerine. Reducing agents like Dibah might well reduce both carbonyl groups and at low temperature could easily stop at the unsaturated aldehyde stage[10]. Additionally compared to the pentacyclic compound (4) this tetracyclic species will show decreased ring strain thus rendering the product much less prone to ring fission and overreduction. Dibah reduction in dry tetrahydrofurane at -70°C in fact gave rise to one more polar product only, but DC behaviour and spectral as well as analytical data immediately ruled out akagerine like structures.

It proved the product to be a dihydro derivative, and as the UV spectrum has changed into normal indole absorption and the NMR pattern of the proton at C_{17} differs from the one in akagerine, structure (8a) is proposed for this compound. The special downfield shift of one aromatic proton additionally indicates a β-hydroxy group located in the plane of the aromatic ring.

As the bulky Lewis acid reducing agent Dibah might be responsible for creating the cis-relationship of the protons at C_{15} and C_{17} we next tried the strongly nucleophilic triethyl borohydride and were pleased to isolate the epimeric carbinol (8b), which proved to be less polar than (8a). The NMR signal of the proton at C_{17} in this case being very similar to the one in akagerine we used this stereoisomer for further elaboration into the natural product. Dibah reduction of this material was not to be stopped at the aldehyde stage and reduction in methylene chloride even at -70°C cleanly produced the unsaturated carbinol (9) which again showed a C_{17} proton resonance very similar to the one in akagerine and which on subsequent nickel peroxide oxydation[11] gave rise to akagerine as proven by comparison with an authentic sample.

Experimental Part

Dilactame (4): 1 g of ester (3b) dissolved in 30 ml methanol is treated with a solution of 1 g sodiumhydroxide in 20 ml water. After 2 h at room temperature the solution is acidified and extracted with methylene chloride. After evaporation of the solvent and vacuum drying of the residue 70 ml trifluoracetic acid anhydride is added and this solution is stirred under nitrogen for 5 h (room temperature). After evaporation the residue is redissolved in aceton and evaporated again for two times. After this treatment crystals are obtained from acetone/ether, 750 mg = 82%, m.p. 199°C. UV (CH_3OH) λ_{max} 245, 270, 295, 305 nm (ε = 16100, 12000, 4800, 4600); IR (KBr) ν_{max} 1710, 1685, 1660, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.03 (1H, m), 7.5-7.1 (3H, m), 7.05 (1H, q, J 7.5 Hz), 4.68 (2H, m), 1.77 (3H, d, J 7.5 Hz); MS (200°C) M^+ 306 ME (100%), 278 (32), 263 (19), 235 (32), 206 (18), 183 (16), 169 (51), 156 (32); $C_{19}H_{18}N_2O_2$ (306.2) calc. C 74.49, H 5.92, N 9.14, found C 74.01, H 5.87, N 9.04.

If acid (5) is treated the same way for 30 min (room temperature) work up as above and thinlayer separation (ether/acetone 9:1) gave rise to crystals of dilactame (6) (44%), m.p. 102°C. UV (CH_3OH) λ_{max} 245, 270, 295, 305 nm (qualitative); IR (KBr) ν_{max} 1725, 1680, 1660, 1620 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.99 (1H, m), 7.48-7.23 (3H, m), 6.02 (1H, q, J 7 Hz), 4.52 (2H, m), 2.10 (3H, d, J 7 Hz); MS (120°C) M^+ 306 ME (24%), 305 (100), 278 (25), 263 (26), 249 (11), 235 (38), 206 (14), 180 (17), 169 (60), 168 (32), 167 (35), 156 (43); $C_{19}H_8N_2O_2$ calc. 306.1368, found 306.1368 (MS).

Further treatment of this material under the conditions given above change it into pure dilactame (4).

Ester (7a): 0.7 g dilactame (4) dissolved in 30 ml dry methylene chloride is treated with 1.7 g triethyloxonium hexafluorophosphate for 12 h at room temperature. Addition of a mixture of methanol (12 ml), water (4 ml), and trifluoracetic acid (4 ml) is followed by extraction with ether (separation of starting material: 120 mg). Subsequent basification and methylene chloride extraction yields 325 mg (48%) of ester (7a), m.p. 143°C. IR (KBr) ν_{max} 1710, 1700, 1640, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.37 (1H, m), 7.54-7.2 (3H, m), 6.95 (1H, q, J 7 Hz), 4.04 (2H, q, J 7 Hz), 1.86 (3H, d, J 7 Hz), 1.01 (3H, tr, J 7 Hz); MS (170°C) M^+ 352 ME (100%), 323 (32), 306 (16), 225 (42), 197 (23), 196 (19), 185 (16), 184 (65), 183 (68), 171 (32), 170 (65), 169 (58); $C_{21}H_{24}N_2O_3$ (352.2) calc. C 71.57, H 6.86, N 7.95, found C 71.36, H 6.94, N 7.84.

N_b-methylation to (7b): 70 mg of (7a) in 4 ml acetic acid is treated with 50 mg formaldehyde (dissolved in methanol). After 10 min the mixture is cooled to 0°C and subsequently a surplus of borohydride is added. After one hour, treatment with surplus soda solution and extraction with methylene chloride yields 63 mg (86%) of the N-methyl derivative (7b), m.p. 154°C. IR (KBr) ν_{max} 1715, 1700, 1640, 1620 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 8.59 (1H, m), 7.51-7.22 (3H, m), 6.91 (1H, q, J 7 Hz), 4.00 (2H, q, J 7 Hz), 2.51 (3H, s), 1.86 (3H, d, J 7 Hz), 1.01 (3H, tr, J 7 Hz); MS (180°C) M^+ 366 ME (29%), 350 (23), 337 (10), 323 (8), 240 (10), 239 (59), 211 (9), 206 (9), 198 (10), 196 (18), 185 (36), 184 (100), 183 (95), 171 (23); $C_{22}H_{26}N_2O_3$ (366.2) calc. C 72.11, H 7.15, N 7.64, found C 72.14, H 6.97, N 7.55.

Carbinol (8a): 74 mg of amine (7b) is dissolved in 9 ml dry tetrahydrofurane and at -70°C treated with 0.3 ml of a Dibah solution in toluene (20%). After 2 h methanol is added and the mixture refluxed for a few minutes. After filtration and evaporation the residue is separated by TLC and one obtains 55 mg (74%) of carbinol (8a), m.p. 132°C. IR (KBr) ν_{max} 3440, 1710, 1635 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.94 (1H, m), 7.56-7.00 (3H, m), 6.65 (1H, q, J 7 Hz), 5.08 (1H, dd, J 7 Hz, J 2 Hz), 4.03 (2H, q, J 7 Hz), 2.37 (3H, s), 1.61 (3H, d, J 7.5 Hz), 1.16 (3H, tr, J 7 Hz); MS (200°C) M^+ 368 ME (27%), 352 (14), 349 (12), 339 (10), 335 (14), 306 (13), 241 (22), 214 (14), 213 (14), 198 (31), 185 (100), 184 (39), 183 (35), 171 (55); $C_{22}H_{28}N_2O_3$ calc. 368.2099, found 368.2099 (MS).

Carbinol (8b): 63 mg of amine (7b) dissolved in 5 ml dry tetrahydrofurane is treated with commercial solution of lithium triethyl borohydride in tetrahydrofurane at room temperature. After stirring for 30 min soda solution is added and the substance isolated by methylene chloride extraction. TLC separation yields 43 mg (68%) of carbinol (8b), m.p. 176°C. IR (KBr) ν_{max} 3400, 1710, 1630 cm^{-1}; ^{1}H-NMR (90 MHz, DMSO-D_6) δ 7.55-6.86 (4H, m), 6.67 (1H, q, J 7 Hz), 6.16 (1H, m), 4.03 (2H, q, J 7 Hz), 2.43 (3H, s), 1.88 (3H, d, J 7 Hz), 1.77 (3H, tr, J 7 Hz); MS (280°C) M^+ 368 ME (28%), 352 (23), 349 (8), 339 (13), 335 (8), 326 (15), 255 (15), 241 (30), 214 (18), 213 (23), 198 (33), 186 (26), 185 (100), 184 (46), 183 (43), 171 (56); $C_{22}H_{28}N_2O_3$ calc. 368.2099, found

368.2099 (MS).

Diol (9): Reduction of 25 mg of carbinol (8b) in 4 ml dry methylene chloride by 0.2 ml of a 20% Dibah solution in toluene at -70°C after work up (see under 8a) yielded 19 mg (88%) of diol (9), m.p. 143°C. IR (KBr) ν 3400, 1610 cm^{-1}; ^{1}H-NMR (90 MHz, acetone-D_6) δ 7.63-7.00 (4H, m), 6.44 (1H, dd, J 4.5 Hz, J 2 Hz), 5.61 (1H, q, J 7 Hz), 4.14 (2H, m), 2.63 (3H, s), 1.86 (3H, d, J 7 Hz); MS (240°C) M^+ 326 ME (24%), 308 (5), 283 (5), 255 (19), 218 (13), 198 (23), 185 (100), 184 (29), 183 (25), 171 (24); $C_{20}H_{26}N_2O_2$ calc. 326.1994, found 326.1945 (MS).

Akagerine (1): Oxydation of 10 mg of diol (9) in 3 ml benzene with a surplus of nickel peroxide by heating for 12 h at 50°C, yields after filtration, evaporation, and TLC separation a substance which proved to be identical with akagerine.

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