A NEW APPROACH TO THE SKELETON OF RAUWOLFIA ALKALOIDS

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The reaction of enamine derivative 2 with ethyl α-acetoxyacrylate gave the indolo[2,3-a]-quinolizidine derivative 3a. From 3a the characteristic structure of the Rauwolfia alkaloids has been built up by stereoselective reactions.

The Rauwolfia alkaloids reserpine, deserpidine and a few semi-synthetic derivatives are widely used drugs for the treatment of high blood pressure and of deseases of psychic origine.

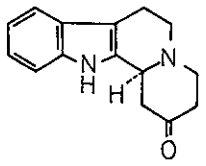
The first ingenious synthesis of reserpine unique up to the present, is linked with the name of Woodward[1] who sol-

ved the problem by a convergent approach.

As has been done in the preparation of yohimbine alkaloids[2a-d] chose a linear method.

The reaction of methyl vinyl ketone with 3,4-dihydro-β-carboline gave rise to the tetracyclic ketone 1 in 45 % yield[3]. The latter compound was converted to the enamine 2 by boiling it in benzene with pyrrolidine [IR(KBr) 3200-3100 (NH), 1660 cm^{-1} (-C=C-N<)]. The crude enamine was treated with methyl α-acetoxyacrylate (2.5 equiv.) in benzene for three days at room temperature in the presence of a small amount of tert. butanol as a proton source. After hydrolysis and chromatographic purification ester 3a was obtained in 27 % yield [mp 206-208°C, IR(KBr) 3400(NH), 1760, 1740(CO), 1250, 1200 cm^{-1} (OAc), NMR (δ in $CDCl_3$) 8.5 (s, 1, NH), 7.9-7.15 (m, 4, aromatic protons), 5.2 (m, 1, CH-OAc), 3.85 (s, 3, CO_2CH_3), 2.18, 2.20 (s, 3, OAc), MS(70eV) m/e 384 (M^+, $C_{21}H_{24}N_2O_5$, base peak), 353, 341, 325, 253, 184, 170, 169]. The doubled acetyl signal in the NMR spectrum proved, that we have 3a as a 1:1 diastereomeric mixture in our hands. But there would have been no advantage in the separation of them in this phase, because in the pentacyclic compound, formed as a result of the subsequent reactions, the hydroxy group is placed in the α-position with respect to the ketone function, so that it can change its configuration relatively freely via the enol form.

Hydrolysis of the acetyl group affords the highly crystalline 3b [mp 142-144°C, IR(KBr) 3350-3150 (NH, OH), 1730 (CO_2CH_3), 1100 cm^{-1} (C-OH), NMR($CDCl_3$) 8.7 (s, 1, NH),



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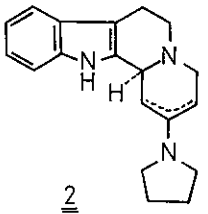

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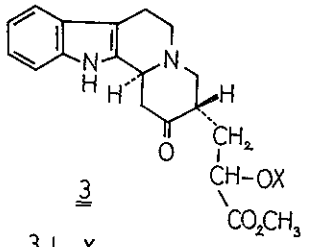
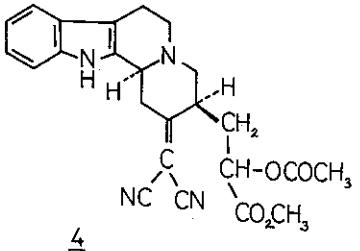


3

3	X
a	$COCH_3$
b	H



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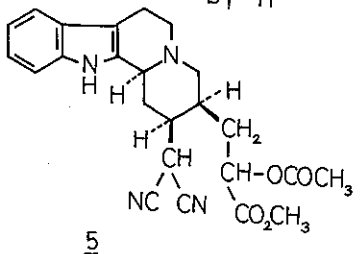

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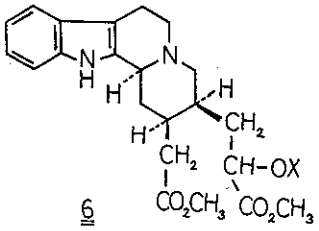
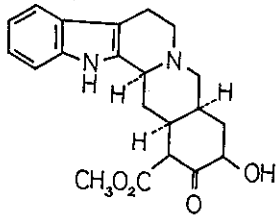


6

6	X
a	H
b	$-CH(OC_2H_5)CH_3$



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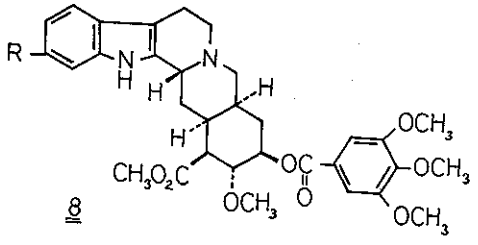

8

Deserpidine R=H (8b)
Reserpine R=OCH_3 (8a)

7.05-7.8 (m, 4, aromatic protons), 3.72 (s, 3, CO_2CH_3)].

3a was condensed with malononitrile in the presence of P_2O_5 in triethylammonium acetate at room temperature for 2-3 hours and the crude product (4) obtained was reduced by $NaBH_4$ furnishing 5 in 80 % yield [4: mp 90-92°C, (amorphous), IR(KBr) 3350 (NH), 2200 ($CN_{conj.}$) 1740-1730 (CO), 1600 ($C{=}C_{conj.}$), 1210 cm^{-1} (OAc), NMR($CDCl_3$) 8.48, 8.43 (s, 1, NH), 7.52-6.98 (m, 4, aromatic protons), 5.1 (m, 1, C<u>H</u>-OAc), 3.65, 3.63 (s, 3, CO_2CH_3), 2.09, 2.07 (s, 3, OAc), MS m/e (M^+, $C_{24}H_{24}N_4O_4$), 431, 401, 389, 384, 341, 301 (base peak), 184, 170, 169; 5: mp 190-192°C, IR(KBr) 3400 (NH), 2250 (CN), 1740 (CO), NMR(DMSO-d_6) 11.0 (s, 1, NH), 7.6-6.85 (m, 4, aromatic protons), 5.1 (m, 1, C<u>H</u>-OAc), 3.64 (s, 3, CO_2CH_3), 2.06 (s, 3, OAc), MS m/e 434 (M^+, $C_{24}H_{26}N_4O_4$), 433, 403, 391, 370 (base peak), 184, 170, 169].

The next six reaction steps were performed without isolation of the intermediates in an overall yield of 60 %(!). They were as follow: a.) $NaOCH_3$/methanol at room temperature for 3 days (furnishing imino ether[2c]), b.) acidification of the solution giving rise to cyano ester, c.) hydrolysis to dicarboxylic acid by 5 % NaOH aq., 12 hr at room temperature, d.) decarboxylation in DMF, 30 min at 120°C in the presence of NaCl, e.) hydrolysis by 10 % NaOH aq., 3-4 hr at boiling temperature, finally f.) esterification by acidic methanol boiling for 4-5 hr [6a: IR(KBr) 3400-3200 (OH, NH), 1720 cm^{-1} (CO_2CH_3), NMR(DMSO-d_6) 11.0 (s, 1, NH), 7.5-6.9 (m, 4, aromatic protons), 3.6 (s, 6, CO_2CH_3), MS m/e 400 (M^+, $C_{22}H_{28}N_2O_5$),

399 (basic, peak), 369, 341, 312, 311, 211, 184, 170, 169].

We were not able to perform a Dieckmann condensation with the obtained 6a because of the free hydroxyl group. But after etherification, i.e. converting 6a to 6b the problem was solved [6b: IR(KBr) 3350 (NH), 2790, 2750 (Bohlmann bands), 1740-1720 cm^{-1} (CO_2CH_3), MS m/e 472 (M^+, $C_{26}H_{36}N_2O_6$), 471, 427, 413, 399 (basic peak), 383, 341, 311, 211, 184, 170, 169].

The ring closure was performed in DMSO/potassium tert. butoxide system (4 days at room temperature) in 75 % yield thus achieving 7 [IR(KBr) 3350 (NH), 1740 (CO_2CH_3), 1660, 1630 cm^{-1}enolic β-keto ester), MS m/e 440 (M^+, $C_{25}H_{32}N_2O_5$), 439, 408, 367 (bäsic peak), 351, 335, 211, 197, 184, 170, 169] which has the basic skeleton of the Rauwolfia alkaloids.

Compound 7 was transformed in several steps to deserpidine (8b) and so the stereostructure was proved. The detailed description of the latter reaction sequences will be the subject of a forthcoming full paper.

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