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# SYNTHESIS OF /±/-YOHIMBINE AND /±/-β-YOHIMBINE. A NEW ROUTE TO YOHIMBAN RING SYSTEM.

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We recently published a new method of synthesis for producing compounds containing an octahydro-indolo-quinolizine skeleton /1/. This method seemed very useful to obtain some intermediate products serving for the synthesis of alkaloids containing pentacyclic indolo/2,3-a/quinolizine ring system, provided the substituents had been appropriately chosen. In this way the synthesis of the substituted yohimban skeleton can be realized more simply than hitherto known / e.g. 2-4/.

The ketone I /b.p. 7o-71° at 3 mm; $n_D^{23}$=1,45oo; $\lambda_{max}^{EtOH}$ 219 m /log 3,85/; $\nu_{max}^{KBr}$ 174o $cm^{-1}$ /$COOCH_3$/, 168o $cm^{-1}$ /CO/; m.p. of dinitrophenylhydrazone 123-124°/ and the quaternary salt II /m.p. 118-119°; Found C 38,24; H 6,11; N 3,85; $C_{11}H_{22}NO_3$J requires C 38,48; H 6,46; N 4,08/ necessary for the new synthesis can be obtained by hydrolyzing 1-acetylglutaric ester /5/ in order to prepare the free carboxylic acid which in turn is reacted with formaldehyde and di-

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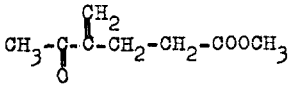
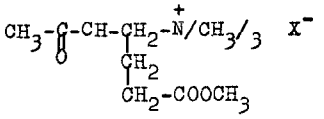


I



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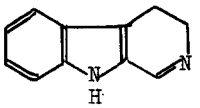
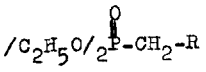
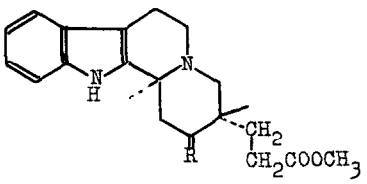


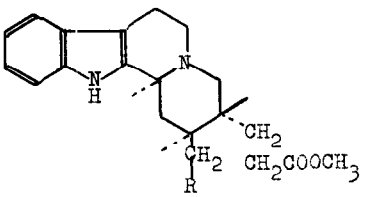
III



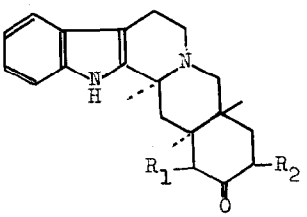
Va R=$COOCH_3$
Vb R=CN



IVa R=O
IVb R=$CHCOOCH_3$
IVc R=CHCN



VIa R=$COOCH_3$
VIb R=CN



VIIa $R_1$=H, $R_2$=$COOCH_3$
VIIb $R_1$=$COOCH_3$, $R_2$=H
VIIc $R_1$=CN, $R_2$=H

methylamine, thereafter esterified with methanol in the presence of hydrochloric acid. The methyl iodide treatment of the Mannich base obtained besides ketone I, afforded the salt II, which on conversion with alkali gave also the ketone I.

On boiling 3,4-dihydro-β-carboline [III, which is obtained in 85,5% crude yield from N-formyl-triptamine] /7/, either with compound I or salt II /cp.8/ in alcohol, derivative IVa [m.p. 208-209°; $\nu_{max}^{KBr}$ 3380 $cm^{-1}$/NH/, 1725 $cm^{-1}$/$COOCH_3$/. Found C 69,83; H 6,54; N 8,61, $C_{19}H_{22}N_2O_3$ requires C 69,61; H 6,79; N 8,58] is obtained in good yield.

Treatment of the latter with the phosphonic acid derivative Va /9/ or Vb /10/ in dimethylformamide in the presence of K.t.butylate gave compounds IVb [m.p. 123-124°/from methanol/; $\nu_{max}^{KBr}$ 1735 $cm^{-1}$/$COOCH_3$/, 1700 $cm^{-1}$ /$COOCH_3$ konj./, 1645 $cm^{-1}$/C=C/. Found C 66,69; H 7,24; N 7,21, $C_{22}H_{26}N_2O_4.CH_3OH$ requires C 66,64; H 7,29; N 6,76] and IVc [m.p. 206-207° /from dioxan-water/, $\nu_{max}^{KBr}$ 3370 $cm^{-1}$ /NH/, 2220 $cm^{-1}$/CN/, 1740 $cm^{-1}$/$COOCH_3$/, 1620 cm-1 /C=C/. Found C 71,67; H 7,29; N 11,61, $C_{21}H_{23}N_3O_2$ requires C 71,77; H 7,17; N 11,96] respectively.

When the unsaturated ester IVb or IVc was hydrogenated in presence of Pd, the corresponding diester VIa [m.p. 155-156°/from petroleum ether/, $\nu_{max}^{KBr}$ 1745 $cm^{-1}$ and 1715 $cm^{-1}$/$COOCH_3$/, $\nu_{max}^{CH_2Cl_2}$ only 1735 $cm^{-1}$/$COOCH_3$/. Found C 68,45; H 7,51; N 7,23, $C_{22}H_{28}N_2O_4$ requires C 86,37; H 7,33; N 7,28] or VIb [m.p. 191-192°/from dioxan-water/, $\nu_{max}^{KBr}$

3355 $cm^{-1}$/NH/, 2260 $cm^{-1}$/CN/, 1730 $cm^{-1}$/$COOCH_3$/. Found C 71,67; H 7,29; N 11,61, $C_{21}H_{23}N_3O_2$ requires C 71,77; H 7,17 N 11,96 ] was obtained.

Treatment of ester VIa in dimethyl sulfoxide with dimsyl-Na /11/ [ Dieckmann condensation in homogenious Phase, cp. 12 ] gives the β-ketoester VIIa [ m.p. 221-223° /from dioxan-water/, $\nu_{max}^{KBr}$ 3395 $cm^{-1}$/NH/, 1740 $cm^{-1}$/$COOCH_3$/, 1710 $cm^{-1}$/CO/, 1655 $cm^{-1}$/chelate enolic form/, 1620 $cm^{-1}$ /C=C/. Found C 69,42; H 7,56; N 7,22, $C_{21}H_{24}N_2O_3$.1/2 $H_2O$ requires C 69,78; H 7,24; N 7,75 ] exclusively, which analogously to the optically active compound /4/ exists in solution mostly in the enol-form. Its structure was proved as follows. After hydrolysis /±/ yohimbone/13/ was obtained, which gave m.p. depression with /±/ alloyohimbone /14/ and its reduction by the Wolf-Kishner-method afforded /±/ yohimban /15/. Furthermore the starting material VIIa was recovered by reacting /±/ yohimbone with magnesium methyl carbonate /4/.

When the condensation of the diester VIa was carried out in heterogeneous phase [ in benzene in the presence of sodium methoxide ] the compound VIIa and the non-enolizable ketoester VIIb [ m.p. 239° /from methanol-water and dried i. vak. at 140°/, $\nu_{max}^{KBr}$ 3395 $cm^{-1}$ /NH/, 1745 $cm^{-1}$/$COOCH_3$/, 1710 $cm^{-1}$/CO/. Found C 71,91; H 6,43; N 8,18; $C_{21}H_{24}N_2O_3$ requires C 71,57; H 6,86; N 7,95 ] were obtained in an approximate ratio of 1:1.

In our opinion the formation of VIIIc is due to a kinetic control with participation of the indole-NH-group /cp. 3/.

Intramolecular condensation of the nitrilester VIb by means of dimsyl-Na gave the ketonitrile VIIc [ m.p. 282-283° /it crystallizes from dioxan with 1 mole dioxane/ ; $\nu_{max}^{KBr}$ 2255 $cm^{-1}$/CN/, 1725 $cm^{-1}$/CO/. Found C 7o,73; H 7,18; N lo,37, $C_{2o}H_{21}N_3O.C_4H_8O$ requires C 7o,65; H 7,18; N lo,3o] in good yields.

Reduction of the β-ketoester VIIb with sodium borohydride an chromatography of the product over alumina /cp. 16/ afforded /±/β-yohimbine and /±/yohimbine in the ratio of about 3:1 ; the only synthesis of the latter compound had been achieved in a quite different route /2/. The infrared spectra of these compounds in chloroform were exactly identical in all respects with those of the natural substances.

Experiments in progress aim at utilizing the epimerization observed in the reaction of "PO-activated compounds" and 2-oxo-benzo/a/quinolizine derivatives /17,18/, in order to build up the alloyohimban skeleton.

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