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SYNTHESIS OF 2,3-DISUBSTITUTED HEXAHYDRO-BENZO/a/QUINOLIZINES AND OCTAHYDRO-INDOLO/2,3-a/QUINOLIZINES

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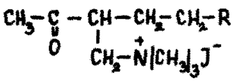
Recently we have published the synthesis of different benzo/a/quinolizine and indolo/2,3-a/quinolizine alkaloids /2,3/. We now wish to report the synthesis of several intermediates, which seem to be useful in the preparation of alloberban and alloyohimban derivates.

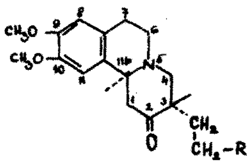
Applying the method of Openshaw and Whittaker /4/, the salt Ia /3/ was reacted with 6,7-dimethoxy-3,4-dihydro--izoquinoline yielding 78 % ester IIa /m.p. 130° /from ethanol/; ν_{max}^{KBr} 1735 /$COOCH_3$/, 1705 /CO/; found C: 66,03; H: 7,34; N: 4,07; $C_{19}H_{25}NO_5$; requires C: 65,79; H: 7,25; N: 4,03./.

The Wittig reaction of IIa with ethoxycarbonilmethylene-triphenilphosphorane at 150° furnished the ester IIIa in 83 % yield /cf. 5,6/ /m.p. 128° /from ethanol/; $_{max}^{KBr}$ 1738 /$COOCH_3$/ 1710 /$COOC_2H_5$ conj./; 1642 /C=C/; found: C: 66,05; H: 7,47; N: 3,67; $C_{23}H_{31}NO_6$; requires: C: 66,16;

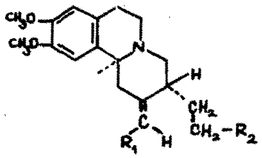


$CH_3-\underset{\overset{\|}{O}}{C}-\underset{\underset{CH_2-\overset{+}{N}(CH_3)_3\,J^-}{|}}{CH}-CH_2-CH_2-R$

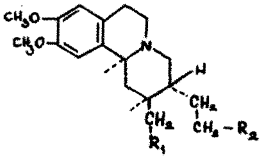
I a: R = $COOCH_3$
b: R = CN



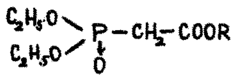
II a: R = $COOCH_3$
b: R = CN



III a: $R_1 = COOC_2H_5$ $R_2 = COOCH_3$
b: $R_1 = COOC_2H_5$ $R_2 = CN$

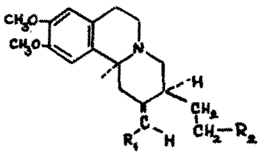


IV a: $R_1 = COOC_2H_5$ $R_2 = COOCH_3$
b: $R_1 = R_2 = COOCH_3$
c: $R_1 = COOC_2H_5$ $R_2 = CN$

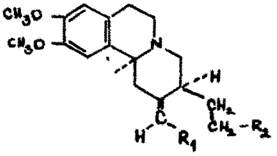


$(C_2H_5O)_2\overset{}{\underset{\downarrow O}{P}}-CH_2-COOR$

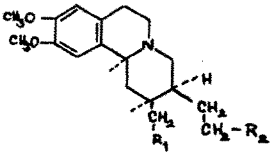
V a: R = C_2H_5
b: R = CH_3



VI a: $R_1 = COOC_2H_5$ $R_2 = COOCH_3$
b: $R_1 = COOC_2H_5$ $R_2 = CN$



VII a: $R_1 = COOC_2H_5$ $R_2 = COOCH_3$
b: $R_1 = COOC_2H_5$ $R_2 = CN$



VIII a: $R_1 = COOC_2H_5$ $R_2 = COOCH_3$
b: $R_1 = COOC_2H_5$ $R_2 = CN$
c: $R_1 = R_2 = COOCH_3$

H: 7,48; N: 3,35/. Catalytic /Pd/C/ hydrogenation of IIIa gave the ester IVa /yield: 57 %/ /m.p. 81° /light petroleum/; ν_{max}^{KBr} 1740 and 1730 /ester CO/; found: C: 66,02; H: 7,89; N: 3,64; $C_{23}H_{33}NO_6$; requires: C: 65,85; H: 7,93; N: 3,34/, /IVa.HCl: m.p. 182° /from methanol-ether/; ν_{max}^{KBr} 1735 and 1715 /ester CO/; found: C: 60,26; H: 7,73; N: 3,21; $C_{23}H_{33}NO_6$.HCl; requires: C: 60,58; H: 7,51; N: 3,07./

The ester IVa was transformed into the dimethylester IVb /m.p. 96-97° /from methanol-water/, ν_{max}^{KBr} 1735 and 1730 /$COOCH_3$/ found: C: 65,18; H: 7,63; N: 3,45; $C_{22}H_{31}NO_6$; requires: C: 65,16; H: 7,71; N: 3,45./ by boiling it in methanol in the presence of sodium methoxide.

When the condensation reaction of IIa was carried out with the reactant Va in DMF, in the presence of excess K-tert.-butoxide, together with IIIa compounds VIa /m.p. 104° /from ethanol/; ν_{max}^{KBr} 1730 /$COOCH_3$/, 1710 /$COOC_2H_5$ conj./, 1640 /C=C/; found: C: 66,23; H: 7,32; N: 3,33; $C_{23}H_{31}NO_6$; requires: C: 66,16; H: 7,48; N: 3,35/, and VIIa /m.p. 101° /from ethanol/; ν_{max}^{KBr} 1740 /$COOCH_3$/; 1715 /$COOC_2H_5$ conj./, 1640 /C=C/; found: C: 66,28; H: 7,42; N: 3,57; $C_{23}H_{31}NO_6$; requires: C: 66,16; H: 7,48; N: 3,35/, were isolated in about 15 % yield.

Catalytic /Pd/C/ hydrogenation of VIa or VIIa in dioxane solution gave the same ester VIIIa /VIIIa.HCl m.p. 179-180° /from methanol-ether/; ν_{max}^{KBr} 1735 and 1730 /ester CO/; found: C: 60,75; H: 7,58; N: 3,24; $C_{23}H_{33}NO_6$.HCl;

requires: C: 60,58; H: 7,51; N: 3,07/, as the only product; the hydrochloride of which depressed the m.p. of hydrochloride of IVa.

The salt Ib /m.p. 143-147° /from methanol-ether/; ν_{max}^{KBr} 2245 /CN/; 1715 /CO/; found C: 38,83; H: 6,12; N: 8,46; I: 40,66; $C_{10}H_{19}N_2OI$; requires: C: 38,72; H:6,17; N: 9,03; I: 40,91/, was prepared from 5-oxocapronic-acid-nitril /7/ by Mannich reaction /formaldehyd + dimethylamine hydrochloride/ and treatment of the obtained base with methyliodide, in 36 % overall yield.

Reaction of 6,7-dimethoxy-3,4-dihydro-izoquinoline base with the salt Ib in boiling methanol furnished the ketone IIb /m.p. 130-131° /from methanol/, ν_{max}^{KBr} 2250 /CN/; 1710 /CO/; found: C: 68,71; H: 6,92; N: 8,99; $C_{18}H_{22}N_2O_3$; requires: C: 68,76; H: 7,05; N: 8,91/, in 64 % yield. The latter was reacted with Va in DMF, in the presence of excess K.tert.-butoxide. Fractional crystallisation of the obtained product from ethanol gave isomers VIb /m.p. 140--141° /from ethanol/, ν_{max}^{KBr} 2245 /CN/; 1715 /$COOC_2H_5$ conj./, 1645 /C=C/; NMR: /in $CDCl_3$/ δ: 6,81 /C-11 proton/, 6,59 /C-8 proton/, 5,86 /olefinic proton/, 4,50 /C-11b proton/, 4,20 /ester methylene protons/, quartet, J=7 c.p.s./, 3,86 /methoxyl protons/, 1,31 /ester methyl protons, triplet, J=7 c.p.s./, found: C: 68,61; H: 7.41; N: 7,33; $C_{22}H_{28}N_2O_4$; requires: C: 68,72; H: 7,34; N: 7,29/, and VIIb /m.p. 131--132°, ν_{max}^{KBr} 2245 /CN/; 1715 /$COOC_2H_5$ conj./, 1640 /C=C/; NMR: /in $CDCl_3$/ δ: 6,61 /aromatic protons/, 5,94 /olefinic proton/, 4,18 /ester methylene protons, quartet, J=7 c.p.s./, 3,85 /methoxy protons/, 1,29 /ester methyl protons, triplet, J=7 c.p.s./, found: C: 68,48; H: 7,42; N: 7,21; $C_{22}H_{28}N_2O_4$; requires: C: 68,82; H: 7,34; H: 7,28/ in 64 % yield together with IIIb obtained in 20 % yield /m.p. 109-110^{o}; ν^{KBr}_{max} 2248 /CN/; 1710 /$COOC_2H_5$ conj./, 1650 /C=C/; NMR: /in $CDCl_3$/ δ: 6,84 /C-11 proton/, 6,61 /C-8 proton/, 5,61 /olefic proton/, 4,42 /C-11b proton/, 4,22 /ester methylene protons, quartet J=c.p.s./, 3,89 and 3,84 /methoxyl protons/, 1,31 /ester methyl protons, triplet, J=7 c.p.s./, found: C: 68,78; H: 7,29; N: 7,27; $C_{22}H_{28}N_2O_4$; requires: C: 68,72; H: 7,34; N: 7,29/. The compound IIIb was identical with the product isolated from the Wittig reaction of IIb with ethoxycarbonilmethylene-triphenilphosphorane /6/.

The stereochemistry of compounds IIIb, VIb, and VIIb was substantiated by n.m.r. date. The aromatic proton at C-11 of ester IIIb /δ=6,84/ and VIb /δ=6,81/ resonates at higher field than that of VIIb /δ=6,61/ due to the deshielding effect of ester-carbonyl group, while the signal of the other aromathic proton /at C-8/ remains unchanged. Furthermore, the ester VIIb gives one singlet for the protons of the methoxyl group in positions 9 and 10 /δ= -3,82/, while they show separate /3 c.p.s./ peaks in compounds IIIb and VIb due to the same effect.

Catalytic /Pd/C/ hydrogenation of compounds VIb and VIIb yielded the nitrilester VIIIb /m.p. 110-111^{o} /from ethanol-water/, ν^{KBr}_{max} 2245 /CN/; 1710 /$COOC_2H_5$/; found:

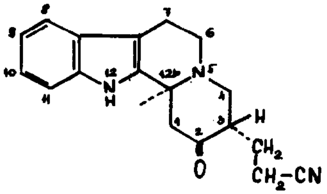
C: 68,43; H: 8,05; N: 7,47; $C_{22}H_{30}N_2O_4$; requires: C: 68,37 H: 7,82; N: 7,25;/ similar treatment of IIIb lead to IVc /m.p. 109° /from ethanol-water/, ν_{max}^{KBr} 2245 /CN/; 1720 /$COOC_2H_5$/; found: C: 68,33; H: 7,59; N: 7,49; $C_{22}H_{30}N_2O_4$; requires: C: 68,37; H: 7,82; N: 7,25/.

On boiling the nitrilester VIIIb in a methanol-sulfuric acid mixture the dimethylester VIIIc /m.p. 63-64° /from light petrolether/, ν_{max}^{KBr} 1740 and 1730 /$COOCH_3$/, found: C: 64,90; H: 7,75; N: 3,57; $C_{22}H_{31}NO_6$; requires: C: 65,16; H: 7,71; N: 3,45/ was obtained in 71 % yield.

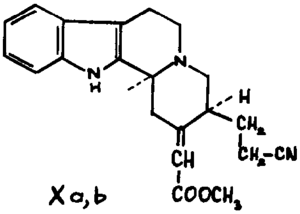
Similar reaction sequences were carried out with the appropriate indol derivatives.

On boiling 3,4-dihydro-β-carboline /8/ with Ib in methanol, the compound IX /m.p. 214-215° /from dioxane-water/, ν_{max}^{KBr} 3370 /NH/; 1705 /CO/; found: C: 73,50; H: 6,50; N: 14,21; $C_{18}H_{19}N_2O$; requires: C: 73,69; H: 6,53; N:14,33/ was obtained in 57 % yield.

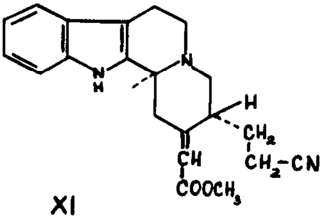
The reaction of ketone IX with Vb in DMF, in the presence of sodium-methoxide at 0° yield a mixture of four isomers in 80 % yield. The components of the mixture could be separated on the basis of their differential solubility in methanol giving to the olefinic-bond cis-trans isomers Xa /m.p. 175-176° /from methanol/, ν_{max}^{KBr} 3370 /NH/; 2245 /CN/; 1710 /$COOCH_3$; conj./, 1640 /C=C/; found: C: 71,91; H: 6,75; N: 11,67; $C_{21}H_{23}N_3O_2$; requires: C: 72,18; H: 6,63; N: 12,03; in 6 % Xb /m.p. 98-125° /from methanol-water/, ν_{max}^{KBr} 3360 /NH/; 2240 /CN/; 1710 /$COOCH_3$ conj./; 1655 /C=C/;



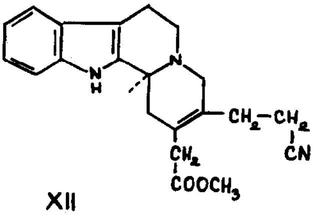
IX



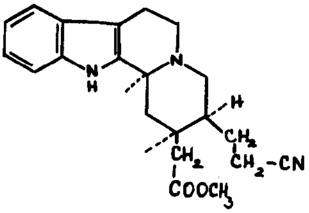
X a,b



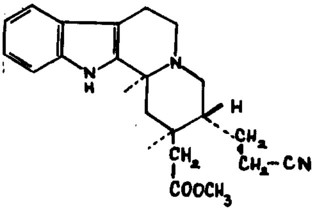
XI



XII



XIII



XIV

found: C: 65,78; H: 6,91; N: 11,40; $C_{21}H_{23}N_3O_2 \cdot 1/5\ H_2O$; requires: C: 67,03; H: 6,96; N: 11,08;/ in 23 %, and XI /m.p. 101° /from methanol/, ν_{max}^{KBr} 3370 /NH/; 2245 /CN/; 1710 /$COOCH_3$ conj./; 1645 /C=C/; found: C: 68,98; H: 6,96; N: 11,05; $C_{21}H_{23}N_3O_2 \cdot CH_3OH$; requires: C: 69,27; H: 7,13; N: 11,02/ in 16 % yield, respectively.

In addition the compound XII, which contains the double bond in an endocyclic position, /9/ was also isolated. /m.p. 194-196° /from dioxane-water/; ν_{max}^{KBr} 3360 /NH/; 2245 /CN/; 1720 /$COOCH_3$/; found: C: 72,05; H: 6,35; N: 12,01; $C_{21}H_{23}N_3O_2$; requires: C: 72,18; H: 6,63; N: 12,03/.

Catalytic /Pd/C/ reduction of Xa and Xb in dioxane solution afferded the same product XIII /m.p. 145-146° /from methanol-water/; ν_{max}^{KBr} 3390 /NH/, 2245 /CN/; 1710 /$COOCH_3$/; found: C: 71,64; H: 7,00; N: 11,85; $C_{21}H_{25}N_3O_2$; requires: C: 71,77; H: 7,17; N: 11,96/.

The hydrogenation of XI in methanol in the presence of Pd/C gave the ester XIV /m.p. 177-178° /from methanol-water/; ν_{max}^{KBr} 3335 /NH/; 2250 /CN/; 1730 /$COOCH_3$/; found: C: 72,02; H: 7,28; N: 11,82; $C_{21}H_{25}N_3O_2$; requires: C:71,77; H: 7,17; H: 11,96./

Further investigations with these compounds are in progress.

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