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A SYNTHESIS OF DIHYDROCORYNANTHEOL AND 3-EPI-DIHYDROCORYNANTHEOL

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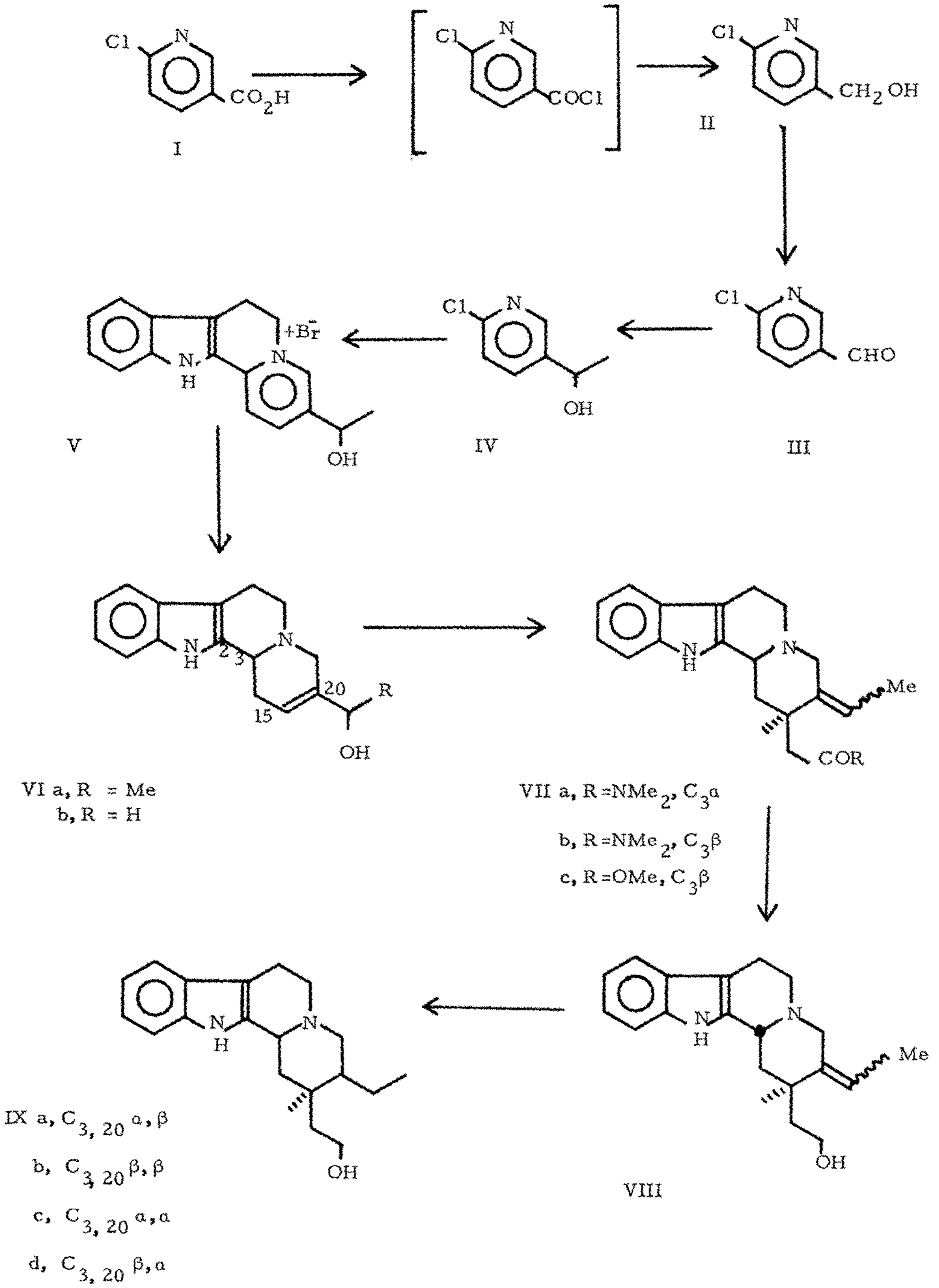
Eschenmoser[2] has demonstrated the efficacy of employing dimethylacetamide dimethylacetal in the Claisen rearrangement, wherein the product is the olefinic dimethylamide as opposed to the traditional olefinic aldehyde. Employing this reaction, we have synthesized dihydrocorynantheol (IXa)[3] and its C_3 epimer, 3-epi-dihydrocorynantheol (IXb).

Treatment of 6-chloronicotinic acid (I)[4] with phosphorus pentachloride/phosphorus oxychloride at reflux followed by reduction of the crude acid chloride in the cold with sodium borohydride afforded 2-chloro-5-hydroxymethyl pyridine (II),[5] mp 39-40°, (89% yield). Oxidation of the alcohol was effected with manganese dioxide in refluxing chloroform,[6] yielding 6-chloro-nicotinaldehyde (III), mp 79-80° (79% yield). Inverse addition of ethereal methyl magnesium bromide to the chloroaldehyde gave 2-chloro-5-(α-hydroxyethyl) pyridine (IV), bp 120-1°/0.15 mm (90% yield).

Alkylation of chloroalcohol IV with tryptophyl bromide according to the procedure of Ban[7] gave the salt V in 27% yield. Reduction with sodium borohydride in aqueous methanol converted the tetracyclic salt to a diastereomeric mixture of allylic alcohols VIa, mp 205-12° dec. (86% yield). The mass spectral pattern $m/_e$ 268 (48), 267 (20), 170 (100), and 169 (60) clearly indicated a retro-Diels Alder-type fragmentation of ring D, confirming the position of the double bond.[8]

Heating the mixture of allylic alcohols with dimethylacetamide dimethylacetal in refluxing dioxane, gave rise to a diastereomeric mixture of amides (VII a and b) in 73% yield, mp. 203-8°. The nuclear magnetic resonance spectrum clearly indicated the presence of two doublets (J = 8 Hz) at 1.70 δ and 1.75 δ corresponding to two olefinic methyls of nearly equal intensity. Separation by thick layer chromatography afforded amide VIIa, mp 210-213°, and VIIb, mp 234-238°. Saponification of the amide mixture with potassium hydroxide in methyl cellosolve followed by direct esterification with methanolic hydrogen chloride afforded ester VIIc, mp 147-151°, in 49% yield as a mixture of double bond isomers (one spot on tlc and a single methyl doublet at 1.65 δ, J = 8 cps.) The same ester could be obtained starting with amide VIIb, in 66% yield.[9]


Cl
N
CO2H
I
COCl
CH2 OH
II
CHO
III
OH
IV
+Br-
N
H
V
OH
2
3
20
15
R
VI a, R = Me
b, R = H
Me
COR
VII a, R =NMe2, C3α
b, R =NMe2, C3β
c, R =OMe, C3β
VIII
IX a, C3, 20 α, β
b, C3, 20 β, β
c, C3, 20 α, α
d, C3, 20 β, α

Reduction of the ester with lithium aluminum hydride in tetrahydrofuran yielded a mixture of 3-epi-geissoschizol (VIII, C_{15}cis) and 3-epi-isogeissoschizol (VIII, C_{15}trans) mp 193-5°, in 86% yield.

It has been demonstrated[10] that catalytic hydrogenation over palladium-charcoal of 3-epi-geissoschizol obtained by C_3 epimerization of geissoschizol (opt.act.) affords 3-epi-dihydrocorynantheol as the major reduction product along with two minor products ($^m/_e$298). When the alcohol mixture VIII was reduced for a prolonged period, two reduction products were formed and separated by thick layer chromatography. The major component was characterized as 3-epi-dihydrocorynantheol (IXb) mp 84-7° (after sublimation of 110°/1 μ) while the minor component was identified as dihydrocorynantheol (IXa), mp 178-180.5° . Comparison of the latter compound with an authentic sample[11](mp 180-182°, mmp 179-181°), showed the two materials to be identical on thin layer chromatography and that they had superimposable infrared spectra. That isomer IXb did have the stereochemistry assigned was based on the knowledge that it was the only unreported racemic stereoisomer, since d, l corynantheidol[12, 13] (IXc, mp 158-160°) and d, l-3-epi-corynantheidol[13](IXd, mp 191-2°) have been reported.

To show that epimerization at C_3 was occurring during hydrogenation, 3-epi-dihydrocorynantheol was subjected to the reduction conditions, giving the same mixture as was obtained during reduction of alcohol mixture VIII. Epimerization of IXb with acetic acid[10] provided a mixture of isomers rich in IXa.

The rearrangement has also been found to be successful with alcohol VIb and 2, 3-seco-VIa.

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3. B. Gilbert, L.D. Antonaccio, and C. Djerassi, J. Org. Chem., 27 4702 (1962).
4. Practical 6-hydroxynicotinic acid (Columbia Chemicals) was purified by conversion to 6-chloronicotinoyl chloride followed by hydrolysis to I. Pure 6-hydroxynicotinic acid (Aldrich) could be employed directly in the preparation of II.
5. All new compounds gave satisfactory elemental analyses and/or mass spectra.
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9. The fate of amide VIIa is not known with certainty. The amide mixture was unaltered (tlc) by treatment with sodium t-amylate in refluxing t-amyl alcohol or by exposure to methanolic hydrogen chloride, indicating that epimerization had not taken place. On the other hand, complete destruction of VIIa is inconsistent with the yields of ester.

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11. We wish to thank Dr. Jerry Weisbach of Smith, Kline, and French for providing us with a sample of d,l-dihydrocorynantheol prepared from the corresponding ester.

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13. E. Wenkert, K.G. Dave, R.G. Lewis, and P.W. Sprague, *J. Am. Chem. Soc.,* **89** 6741 (1967). This compound is referred to as d,l-3-isocorynantheidol. We have used the terminology *epi-* since we have employed the prefix *iso-* in reference to the double bond isomers.