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THE SYNTHESIS OF 1-METHYL-16-DEMETHOXY-CARBONYL-20-DESETHYLIDENEVOBASINE

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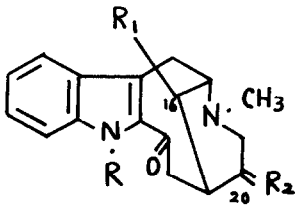
We wish to communicate the first synthesis of 1-methyl-16-demethoxy-carbonyl-20-desethylidenevobasine(I) having the carbon skeleton of the 2-acylindole alkaloids which are represented by vobasine(II)(1).



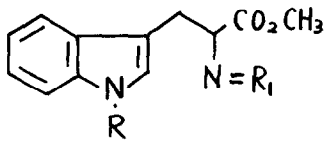
I : R=CH_3, R_1=H, R_2=H,H

II : R=H, R_1=CO_2CH_3, R_2=$CHCH_3$

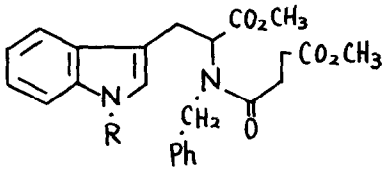
Catalytic hydrogenation of N-benzylidenetryptophan methyl ester(IIIa) (2,3) and its 1-methyl derivative(IIIb) with platinum oxide in methanol afforded respectively N-benzyltryptophan methyl ester(IVa, hydrochloride: m.p. 188°(decomp.)) and its 1-methyl derivative(IVb, hydrochloride: m.p. 232-233°(decomp.))(4) in nearly quantitative yield. The Schotten-Baumann reaction of the esters(IVa,b) with methyl 3-(chloroformyl)propionate gave the dimethyl esters(Va: m.p. 135-135.5°, Vb: viscous oil(4)), which were respectively subjected to the Dieckmann cyclization reaction with sodium hydride in hot dioxane to give the methyl β-keto-esters(VIa: m.p. 144-145°,

VIb: m.p. 153-154.5°) in 80% yield. The corresponding benzyl β-keto-esters (VIIa; m.p. 160-162°, VIIb: m.p. 119-120°) were obtained by heating VIa,b in benzyl alcohol at 170°(bath temp.) for 6 hr. in 80-90% yield. Alkylation of VIIa,b with benzyl bromoacetate in boiling acetone in the presence of potassium carbonate followed by debenzylation and decarboxylation by catalytic hydrogenation over palladium-carbon in ethanol or tetrahydrofuran gave the carboxylic acids(VIIIa: m.p. 212-213°(decomp.), VIIIb: m.p. 186-188°, 80-90% yield from VIIa and VIIb), but it was not clear whether they were diastereoisomeric mixtures or not. VIIIa was converted by the Huang-Minlon reduction to IXa(m.p. 225-227°(decomp.), 49.1% yield) but again it was not clear whether or not a diastereoisomeric mixture was formed. The Huang-Minlon reduction of VIIIb produced a diastereoisomeric mixture which was separated by acetone into IXb-1(m.p. 191-193°, 19.6% yield) and IXb-2(m.p. 233-234°(decomp.), 27.4% yield).

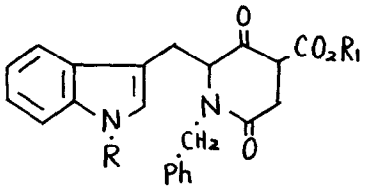
To complete the construction of the molecular framework present in the compound(I) the eight-membered ring had to be closed by an intramolecular cyclization which was performed by the action of polyphosphoric acid (100°, 30 min.) on IXa and IXb-1(5), based on our finding on the synthetic method of cycloalkan[b]indolones(6). The resultant tetracyclic ketolactams (Xa: m.p. 240-242°, 11.4% yield; Xb: m.p. 194-195°, 56.8% yield) exhibited the infrared(Xa: $\nu_{C=O}^{CHCl_3}$ 1633 cm^{-1}, Xb: $\nu_{C=O}^{CHCl_3}$ 1630 cm^{-1}) and ultraviolet spectra (Xa: $\lambda_{max}^{90\%\,EtOH}$ mμ(ε): 235(9,800), 317(14,900), Xb: $\lambda_{max}^{90\%\,EtOH}$ mμ(ε): 238(16,100), 316(19,600)) typical of a 2-acylindole(1,6). Reduction of Xa,b with lithium aluminum hydride in refluxing tetrahydrofuran yielded the alcohols(XIa,b), which were oxidized to the ketones(XIIa: m.p. 211-212°, XIIb: m.p. 166-168°) using chromium trioxide in pyridine at room temperature. The ketones(XIIa,b), which also showed the typical infrared and ultraviolet spectra of a 2-acylindole(1,6), resisted the catalytic debenzylation over palladium-carbon, and only XIIb yielded a small amount of the base(XIIIb), m.p. 257-258°. It was found from spectral data that XIIIb existed predominantly in the form of carbinolamine(XIVb) both in solid and solution states(ν_{OH}^{KBr} 3555 cm^{-1}, $\lambda_{max}^{90\%\,EtOH}$ mμ(ε): 227.5(31,800), 285(6,770), $\lambda_{shoulder}^{90\%\,EtOH}$ mμ(ε): 292(6,450),



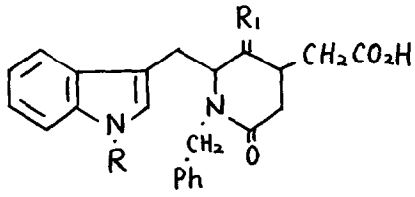
IIIa : R=H, R_1=CHPh
b : R=CH_3, R_1=CHPh
IVa : R=H, R_1=H,CH_2Ph
b : R=CH_3, R_1=H,CH_2Ph



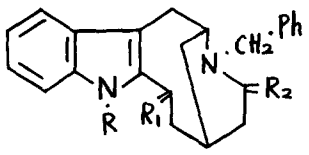
Va : R=H
b : R=CH_3



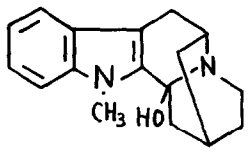
VIa : R=H, R_1=CH_3
b : R=CH_3, R_1=CH_3
VIIa : R=H, R_1=CH_2Ph
b : R=CH_3, R_1=CH_2Ph



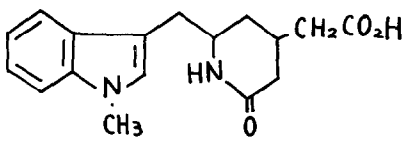
VIIIa : R=H, R_1=O
b : R=CH_3, R_1=O
IXa : R=H, R_1=H,H
b : R=CH_3, R_1=H,H



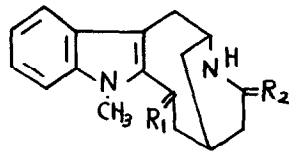
Xa : R=H, R_1=O, R_2=O
b : R=CH_3, R_1=O, R_2=O
XIa : R=H, R_1=H,OH, R_2=H,H
b : R=CH_3, R_1=H,OH, R_2=H,H
XIIa : R=H, R_1=O, R_2=H,H
b : R=CH_3, R_1=O, R_2=H,H



XIVb



XVb



XIIIb : R_1=O, R_2=H,H
XVIb : R_1=O, R_2=O
XVIIb : R_1=H,OH, R_2=H,H

316(2,490))(7).

Thus IXb-1 was first debenzylated with sodium in liquid ammonia(8) to give XVb, which was successively treated as above with polyphosphoric acid, lithium aluminum hydride and chromium trioxide to give the carbinolamine (XIVb) through the steps of XVIb(m.p. 269-270°) and XVIIb(m.p. 218-221°). The synthesis was completed by the action of formalin in the presence of formic acid on XIVb which afforded the desired tetracyclic compound(I, m.p. 163.5-164°, $\nu_{C=O}^{CHCl_3}$ 1642 cm^{-1}, $\lambda_{max}^{90\%EtOH}$ mμ(ε): 239(16,100), 316(18,700))(9).

The mass spectral fragmentation pattern of I(m/e: 282(parent peak), 186, 158, 144, 110, 109, 97, 96(base peak), 95, 94) is very similar to that of vobasine(II)(1,10). This fact confirms that the compound(I) has the same carbon skeleton as that of vobasine(II)(11).

This synthesis will serve as a model for the total synthesis of vobasine (II) and related 2-acylindole alkaloids.

ACKNOWLEDGEMENT

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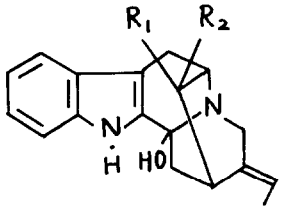
press.

(7) The similar carbinolamine structures were assigned to epiperivine(A) (M. Gorman and J. Sweeny, Tetrahedron Letters, 1964, 3105) and voacarpine(B) (M. Denayer-Tournay, J. Pecher, R. H. Martin, M. Friedmann-Spiteller, and G. Spiteller, Bull. Soc. Chim. Belges, 74, 170 (1965)).



A : R_1=H, R_2=CO_2CH_3

B : R_1=CO_2CH_3, R_2=CH_2OH

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