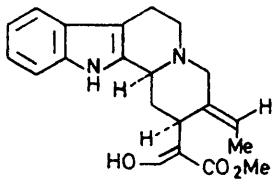
# Total Synthesis of the Alkaloid (±)-Geissoschizine

By KIOYOYUKI YAMADA,* KOZO AOKI, TETSUYA KATO, and DAISUKE UEMURA
(*Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan*)
and EUGENE E. VAN TAMELEN
(*Department of Chemistry, Stanford University, Stanford, California* 94305)

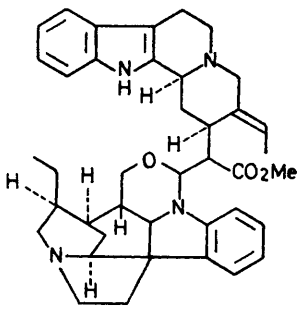
*Summary* A total synthesis of (±)-geissoschizine (**1**) has been carried out starting from tryptamine and ethyl acetyl(cyclopent-3-enyl)acetate.

GEISSOSCHIZINE[1,2] has recently emerged as an early known base which serves in indole alkaloid biosynthesis as a pivotal intermediate,[3,4] being converted into the many various *Strychnos*, *Aspidosperma*, and *Iboga* polycyclic types. Herein we describe the first total synthesis of (±)-geissoschizine (**1**), by means which also reveal the geometry of the ethylidene group. Moreover, the synthesis embraces in principle the more complex naturally occurring system geissospermine (**2**), which results when geissoschizine is condensed with geissoschizoline,[1,2] and which has itself been obtained in the (±)-form by total synthesis.[5]

Alkylation of ethyl acetoacetate with cyclopent-3-enyl tosylate ($Bu^tOK$ in refluxing $Bu^tOH$) afforded (59%) the ester (**3a**), b.p. 125—128° at 16 mm Hg, which on reduction with $NaBH_4$ in EtOH gave (84%) the β-hydroxy ester (**3b**) as a mixture of diastereoisomers, b.p. 129—132° at 14 mm-Hg.† The crude tosylate of (**3b**) (*p*-TsCl/pyridine) was treated with $Bu^tOK$–$Bu^tOH$ at about room temperature for 6 h, yielding [85% from (**3b**)] the β-elimination product, as a mixture of geometrical isomers, b.p. 55—64° at 0·35 mmHg,




(1)

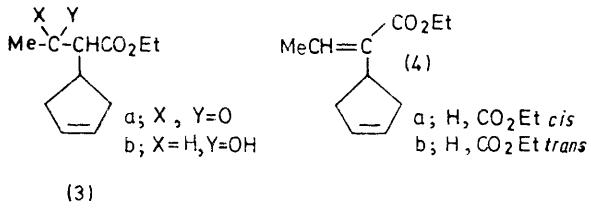



(2)

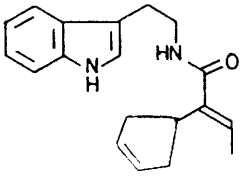
which was separated by preparative t.l.c. into (**4a**) (*cis*) and (**4b**) (*trans*) in a 2:1 ratio, δ ($CCl_4$) (**4a**): 1·79 (3H, d, *J* 7·3 Hz) and 6·70 (1H, q, *J* 7·3 Hz); (**4b**): 1·78 (3H, d, *J* 7·3 Hz) and 5·85 (1H, q, *J* 7·3 Hz). Assignment of the δ 6·70 and 5·85 signals as vinyl hydrogen *cis* and *trans* to ester, respectively, was corroborated by shift values

† All distilled or crystalline intermediates gave satisfactory elemental analyses or mass spectral data.

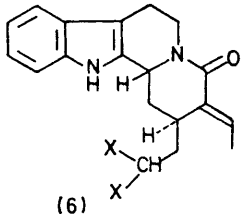
obtained with Eu(fod)$_3$ (**4a**): 0·23 (MeC=) and 1·15 (H–C=C–CO–); (**4b**) 0·32 (MeC=) and 0·36 (H–C=C–CO–).




After saponification of (**4a**) to the corresponding acid, m.p. 148—150°, [convertible by $CH_2N_2$ into the original ester, as was the isomeric acid from (**4b**)], the *p*-nitrophenyl ester, m.p. 60—61°, was prepared (dicyclohexylcarbodi-imide in EtOAc) and then condensed with tryptamine in tetrahydrofuran (THF) to give (87%) the tryptamide (**5a**), m.p. 89—90°. Hydroxylation of amide (**5a**) with $OsO_4$ in THF–pyridine at −70° provided the corresponding cyclopentane-1,2-diol (**5b**) (90% yield of amorphous solid after chromatography on silica), which was directly oxidized by metaperiodate in acetone–$H_2O$ or periodic acid in aqueous $HCO_2Na$–$HCO_2H$. The resulting non-crystalline aldehyde was heated at 60° for 30 min in acetone–0·05N-HCl, giving the oily lactam aldehyde (**6a**), unstable but convertible into the ethylene acetal (**6b**), m.p. 207—208° [69% overall yield from (**5b**)].



(5a)



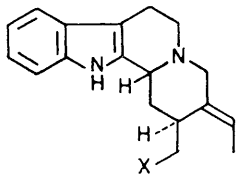
(6)

a: X,X=O

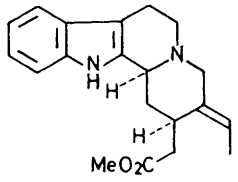
b: X,X=O, O

$NaBH_4$ in EtOH transformed the aldehyde (**6a**) into the corresponding lactam alcohol, m.p. 244—245°, which was reduced by $AlH_3$[6] in THF–glyme to (±)-epigeissoschizol (**7a**) (66%), m.p. 202—204° (decomp.), from which (13%) amorphous (±)-19,20-dihydroepigeissoschizol [also obtained by catalytic reduction of (**7a**)] was separated by preparative t.l.c. The C-3 (*-epi*)stereochemistry in (**7a**) was revealed by Bohlmann i.r. bands (KBr) at 2700—2800 cm$^{-1}$ as well as by oxidation with $Hg(OAc)_2$[7] in THF–AcOH–$H_2O$ to (±)-3-dehydrogeissoschizol. Reduction of the crude salt with Zn in AcOH provided (±)-epigeissoschizol (31%) and (±)-geissoschizol, m.p. 190—194° (decomp.) (27%) indistinguishable from natural geissoschizol.[1,2,8]

The lactam (**6b**) was reduced with $AlH_3$ in THF at 0° to the acetal (**7b**), m.p. 94—96°, obtained in 90% yield after removal of a small amount of 19,20-dihydro-(**6b**). The acetal portion was hydrolysed with *ca.* 1N-HCl at room temperature for 20 h, to give (96%) epi-geissoschizal (**7c**), m.p. 116—118·5. $Ag_2O$ oxidation provided the carboxylic acid, which underwent Fischer esterification to give methyl (±)-epigeissoschizoate (**7d**), m.p. 134—136°. When compound (**7d**) was subjected to the $Hg(OAc)_2$ oxidation–Zn reduction sequence above, but without isolation of the $\Delta^3$ intermediate, methyl (±)-epigeissoschizoate (70%) and the oily methyl (±)-geissoschizoate (**8**) [8%, or 25% based on



(7)



(8)

a; X=HOCH$_2$

b; X = CH$_2$O, CH$_2$O, CH

c; X=OCH

d; X=MeO$_2$C

(**7c**) utilized] were formed. Formylation of the ester (**8**) by treatment with methyl formate in the presence of lithium di-isopropylamide in anhydrous THF (−30 to −15° for 1 h) gave (56%) (±)-geissoschizine, m.p. 187—189° (sealed tube) (from EtOH). The i.r., u.v., n.m.r., and mass spectral, as well as t.l.c. properties of synthetic ester, were identical to those of natural geissoschizine.

Financial support was provided by a National Science Grant to Stanford University. We also thank Professor H. Rapoport, University of California at Berkeley, for a gift of geissospermine, and Dr. J. L. Pousset, Faculté de Pharmacie de Paris, for a sample of geissoschizal.

(*Received, 20th August* 1974; *Com.* 1083.)

[1] H. Rapoport, R. J. Windgassen, Jr., N. A. Hughes, and T. P. Onak, *J. Amer. Chem. Soc.*, 1960, **82**, 4404.
[2] M-M. Janot, *Tetrahedron*, 1961, **14**, 113.
[3] A. A. Qureshi and A. I. Scott, *Chem. Comm.*, 1968, 947.
[4] A. I. Scott, *Accounts Chem. Res.*, 1970, **3**, 151.
[5] (a) B. A. Dodson and J. Harley-Mason, *Chem. Comm.*, 1969, 665; (b) J. Harley-Mason and C. G. Taylor, *ibid.*, 1970, 812.
[6] N. M. Yoon and H. C. Brown, *J. Amer. Chem. Soc.*, 1968, **90**, 2927.
[7] N. J. Dastoor, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 213.
[8] J. L. Poussett, *Trav. Lab. Matiere Med. Pharm. Galenique Fac. Pharm. Paris*, 1967, **52 II**, 13 (*Chem. Abs.*, 1969, **70**, 88034).