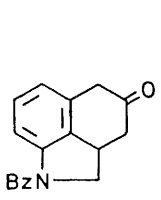
Photocyclisation of Enamides. Part 16.[1] A New Synthesis of Clavines. The Stereostructure of Costaclavine [2]

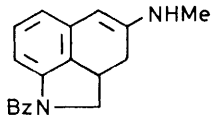
By **Ichiya Ninomiya,*** **Toshiko Kiguchi**, and **Takeaki Naito**, Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan

Epimeric 6,8-dimethylergolines (VI), (VII), and (IX) have been synthesised from the lactam (IVa) which was prepared by the reaction of the enamine (II) with methacryloyl chloride or methacrylamide. The stereochemistry of costaclavine (VI) has been established by comparison of the n.m.r. spectra of compounds (VI), (VII), (IX), and (X).

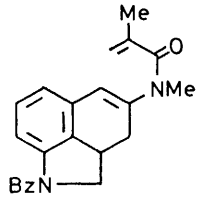
COSTACLAVINE is an alkaloid, first isolated from the saprophytic culture of the agropyrum-type ergot fungus [3] and later also obtained chemically by the reduction of agroclavine and elymoclavine.[4] This chemical conversion made possible the proposal of structure (VI) for costaclavine though its stereochemistry remained to be determined, since a C(8) (VII) of the alkaloid (VI) was not isolated.



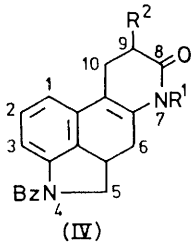
(I)



(II)

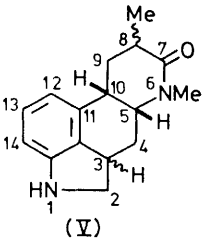


(III)

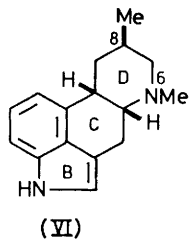


(IV)

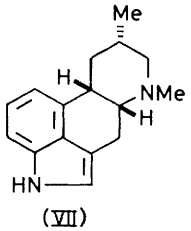
a; $R^1 = R^2 = Me$
b; $R^1 = Me, R^2 = H$
c; $R^1 = H, R^2 = Me$
d; $R^1 = R^2 = H$



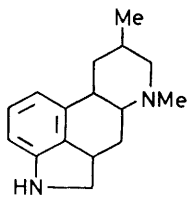
(V)



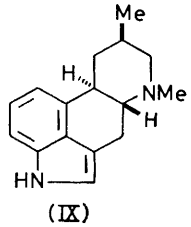
(VI)



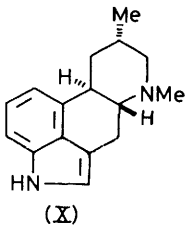
(VII)



(VIII)



(IX)



(X)

We have previously reported the reaction of imines and αβ-unsaturated acid chlorides [5] or acrylamides [6] as a useful method for the preparation of heterocyclic ring systems. This has been applied to the synthesis of a common key intermediate lactam (IVa), which was then employed for a ready synthesis of costaclavine (VI) and its epimers (VII) and (IX). Extensive investigation of the n.m.r. spectra of costaclavine (VI) and the related clavines (VII), (IX), and (X) unambiguously established the stereochemistry of costaclavine.

Synthesis of Costaclavine (VI), *Epidostaclavine* (VII), *and Festuclavine* (IX).—The enamine (II), which was prepared from 1-benzoyl-2,2a,3,5-tetrahydrobenz[*cd*]-indol-4(1*H*)-one (I) [7] and methylamine, was readily acylated with methacryloyl chloride in the presence of triethylamine with cooling by ice. We expected to obtain the methacryloylenamine (III) for use in photocyclisation. However, the products (52%) were a 2 : 1 inseparable mixture of the enamide (III) and the cyclised lactam (IVa). The n.m.r. spectrum of the mixture showed peaks at δ 1.97br (2 H, d, C=CMe) of the enamide (III) and 1.30 (1 H, m, 9-Me) of the lactam (IVa). The latter signal suggested the presence of epimers at the 5a-position. When acylation was carried out in the absence of base in boiling benzene, the yield of the mixture was improved (66%) with an increased ratio (4 : 1) of the lactam (IVa) over the enamide (III). Further, acylation of the enamine (II) with acryloyl chloride, in the absence of base, afforded the lactam (IVb) as the sole product in 38% yield. Attempts to cyclise the enamide (III) to the lactam (IVa) under photochemical and thermal conditions were unsuccessful, giving only tar. Thus, it was found that the reaction of the enamine (II) with αβ-unsaturated acid chlorides gave the enamide (III) and/or the cyclised lactams (IVa and b) depending upon the reactivity of the β-position of the unsaturated acid chlorides and the reaction conditions.[5]

In order to improve the yield of the lactam (IVa), we then investigated the aza-annelation of the enamine with acrylamides as reported previously.[6] Heating a mixture of the enamine (II) and methacrylamide in the presence of toluene-*p*-sulphonic acid at 150° for 2 h afforded the lactam (IVc) as the sole product in 47% yield, as expected.

A similar reaction of the enamine (II) with acrylamide gave the lactam (IVd) as the sole product in 52% yield.

These lactams (IVc and d) were methylated with methyl iodide in the presence of sodium hydride to give the *N*-methyl-lactams (IVa and b) respectively, which were identical with the lactams prepared by the reaction of the enamine (II) with αβ-unsaturated acid chlorides.

The conversion of the lactam (IVa) into 6,8-dimethylergolines was then undertaken according to the procedure given for benzo[*f*]quinoline.[8] Hydrogenation of the lactam (IVa) in the presence of platinum oxide at room temperature and 5 atm pressure, followed by hydrolysis to remove the benzoyl group, gave a mixture of stereoisomers of the saturated lactam (V) in 59% yield. Without further separation, the lactam (V) was reduced with lithium aluminium hydride and subsequently dehydrogenated with manganese dioxide to afford two isomeric 6,8-dimethylergolines (VI) and (VII) in 16 and 4% yields respectively, which were separated by chromatography. The major product (VI) was identical with natural costaclavine [3] upon direct comparison. The n.m.r., i.r., and mass spectral data of the minor product showed that it was not identical with any of three known clavines, costaclavine,[3] pyroclavine,[9] and festuclavine.[10] We therefore suggest structure (VII), an 8-methyl epimer of costaclavine. This fourth isomer (VII) of 6,8-dimethylergoline may exist in nature though it has not hitherto been isolated. Therefore, we have tentatively designated it as epicostaclavine.

Successive reductions of the lactam (IVa) with lithium aluminium hydride and sodium in liquid ammonia gave a mixture of the stereoisomers of the amine (VIII), which was then dehydrogenated with manganese dioxide to afford the crystalline *trans*-clavine (IX) in 22% yield from (IVa). This clavine (IX) was identical with festuclavine upon direct comparison.[10] Costaclavine (VI) and epicostaclavine (VII) were also isolated in low yield by preparative t.l.c. of the mother-liquor of the above reaction, though pyroclavine (X) could not be detected.

Stereochemistry of Costaclavine (VI).—The stereochemistries of two isomers of C/D-*trans*-6,8-dimethylergolines, festuclavine (IX) and pyroclavine (X), have already been unambiguously established by direct comparison.[4,9,10] On the other hand, the absence of an epimer of the C/D-*cis*-clavines has left the establishment of the stereochemistry of costaclavine (VI) yet to be determined, though a recent report by Nakahara *et al.*[11] suggested a preferred conformation from chemical evidence. The isolation of the fourth isomer of 6,8-dimethylergoline, epicostaclavine (VII), enabled us to carry out a thorough investigation of the conformation and stereochemistry of the 6,8-dimethylergolines (VI), (VII), (IX), and (X) by comparison of their n.m.r. spectra using decoupling techniques. The results are summarised in the Table, which contains the following important clues concerning the stereochemistry of the clavines.

Proton chemical shifts (δ) and coupling constants [a] (Hz)

Proton	Costaclavine (VI)	Epicostaclavine (VII)	Festuclavine [b] (IX)	Pyroclavine (X)
9ax-H	1.43 (ddd, *J* 14, 11, 5)	1.20br (q, *J* 12)	1.08br (q, *J* 12)	1.67 (td, *J* 12, 5)
4ax-H	2.88 [c] (ddd, *J* 15, 4, 2)	2.96 (d, *J* 8)	2.68 (dd, *J* 15, 11.5)	2.57 (ddd, *J* 15, 12, 2)
4eq-H	3.20 (dd, *J* 15, 4)		3.39 (dd, *J* 15, 5.4)	3.40 (dd, *J* 15, 4.5)
CMe	0.93 (d, *J* 6)	0.91 (d, *J* 6)	0.99 (d, *J* 6.5)	1.29 (d, *J* 6.5)
NMe	2.24 (s)	2.57 (s)	2.49 (s)	2.36 (s)

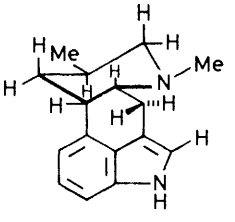
[a] Measured in $CDCl_3$ and data were in agreement with those reported for related compounds; L. Zetta and G. Gatti, *Tetrahedron*, 1975, **31**, 1403. [b] N.m.r. spectrum at 90 MHz by Bach *et al.*[9] [c] On irradiation of the 2-H signal (δ 6.77), the 4ax-H signal was reduced to a double doublet (*J* 15 and 4 Hz).

(1) The similarity of the chemical shifts of the 8-methyl group in costaclavine (δ 0.93) and epicostaclavine (δ 0.91) to that (δ 0.99) of festuclavine showed that the 8-methyl group is equatorial in all three cases. On the other hand, the signal for the 8-methyl group in pyroclavine (X) appeared at δ 1.29 as a result of the deshielding effect due to a 1,3-diaxial interaction with the lone-pair electrons on nitrogen, thus suggesting an axial 8-methyl group, as already established.[3,9,10] These results are in agreement with those for the quinolizidine compounds reported by Moynehan.[12]

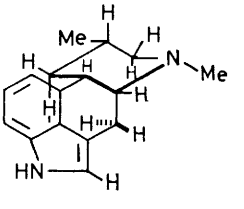
(2) Upon irradiation of the 2-proton signal at δ 6.77 in costaclavine, the signal at δ 2.88 was reduced to a doublet of doublets with *J* 15 and 4 Hz, assigned to 4ax-H, long-range coupled to 2-H. This also suggests an equatorial conformation of 5-H relative to ring C.

(3) Inspection of a Dreiding model of epicostaclavine (VII) suggests an axial conformation of 5-H from the coupling pattern of 4-H_2 which appeared at δ 2.96 as a doublet.

(4) The signals of the *N*-methyl group in costaclavine (VI) appeared at δ 2.24 which is rather to higher field than for other alkaloids probably due to the anisotropy of ring B. This can be explained by assuming that costaclavine exists in conformation (A). The coupling pattern



(A)



(B)

of the 9-axial protons in costaclavine and epicostaclavine suggest conformations (A) and (B) respectively.

Therefore, we conclude that costaclavine has the conformation shown in (A) with the indole ring axial and the 8-methyl group equatorial with respect to ring D, while epicostaclavine has an equatorial 8-methyl group.

EXPERIMENTAL

I.r. spectra were recorded for solutions in chloroform and ^1H n.m.r. spectra for solutions in deuteriochloroform on

Varian A-60D and NEVA NV-21 (90 MHz) instruments (tetramethylsilane as internal reference). M.p.s were determined with a Kofler-type hot stage apparatus. Photochemical experiments were carried out as described previously.[1]

Reaction of 1-*Benzoyl*-4-*methylamino*-1,2,2a,3-*tetrahydrobenz*[cd]*indole* (II) *and Methacryloyl Chloride*.—(a) *At low temperature*. Anhydrous methylamine gas was bubbled into a boiling solution of 1-benzoyl-2,2a,3,5-tetrahydrobenz[*cd*]indol-4(1*H*)-one [7] (I) (2 g) in benzene (200 ml) for 3 h. Water was removed as it formed. Refluxing was continued, to remove the excess of methylamine by bubbling in dry nitrogen. To the above solution triethylamine (1 g) and a solution of methacryloyl chloride (1.5 g) in benzene (50 ml) were added dropwise successively under cooling. After refluxing for 1 h, the mixture was cooled, washed with water, and dried. The solvent was evaporated to give the residue which was chromatographed on silica gel. Elution with chloroform gave a yellow oil (1.4 g, 52%), which was homogeneous on t.l.c. but found to be a mixture of 1-benzoyl-1,2,2a,3-tetrahydro-4-(*N*-methyl-2-methylacrylamido)benz[*cd*]indole (III) and 4-benzoyl-5,5a,6,8,9,10-hexahydro-7,9-dimethylindolo[4,3-*fg*]quinolin-8(4*H*)-one (IVa) in a *ca.* 2 : 1 ratio from the n.m.r. spectrum, $\nu_{max.}$ 1 640—1 660 (NCO) cm^{-1}, δ 6.67br (2/3 H, HC=CN), 5.27 (4/3 H, m, H_2C=C–CO), 3.18 (3 H, s, NMe), 1.97br (2 H, d, C=CMe), and 1.30 (1 H, m, CH*Me*).

(b) *At elevated temperature*. To a benzene solution of the enamine (II) prepared from the ketone (I) (2 g) as in (a), a solution of methacryloyl chloride (1.8 g) in benzene (50 ml) was added dropwise under refluxing. After refluxing for 1 h, the mixture was cooled and filtered. The filtrate was evaporated to give a residue which was chromatographed on silica gel. Elution with chloroform gave a yellow oil (1.8 g, 66%), which was shown to be an inseparable mixture of the enamide (III) and the lactam (IVa) in a *ca.* 1 : 4 ratio from the n.m.r. spectrum.

4-*Benzoyl*-5,5a,6,8,9,10-*hexahydro*-7-*methylindolo*[4,3-fg]-*quinolin*-8(4H)-*one* (IVb).—By the procedure given for (IVa), the reaction of the enamine (II) prepared from the ketone (I) (1.5 g) and acryloyl chloride (1.5 g) in boiling benzene (50 ml) under nitrogen afforded the *lactam* (IVb) (700 mg, 38%) as the sole product, m.p. 171—173° (from methanol), $\nu_{max.}$ 1 655 (NCO) cm^{-1}, δ 3.15 (3 H, s, NMe) and 2.65br (4 H, s, 9- and 10-H_2) (Found: C, 76.95; H, 5.95; N, 7.95. $C_{22}H_{20}N_2O_2$ requires C, 76.7; H, 5.85; N, 8.15%).

4-*Benzoyl*-5,5a,6,8,9,10-*hexahydro*-9-*methylindolo*[4,3-fg]-*quinolin*-8(4H)-*one* (IVc).—A mixture of the enamine (II), prepared from the ketone (I) (1 g), methacrylamide (600 mg), and toluene-*p*-sulphonic acid (a small amount), was heated at 150° for 2 h with stirring under nitrogen. Water was added and the aqueous layer was extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was recrystallised from methanol to afford the *lactam* (IVc) (300 mg, 47%) as a brown powder, m.p. >300° (decomp.), $\nu_{max.}$ 1 680 (NCO) cm^{-1} (Found: C, 76.35; H, 6.0; N, 8.0. $C_{22}H_{20}N_2O_2$ requires C, 76.7; H, 5.85; N, 8.15%).

4-*Benzoyl*-5,5a,6,8,9,10-*hexahydroindolo*[4,3-fg]*quinolin*-8(4H)-*one* (IVd).—According to the procedure given for (IVc), a mixture of the enamine (II), prepared from the ketone (I) (100 mg), acrylamide (60 mg), and toluene-*p*-sulphonic acid (a small amount) was heated at 150° for 2 h to give the *lactam* (IVd) (50 mg, 52%), as a pale brown powder, m.p. 215—218° (from methanol), $\nu_{max.}$ 1 655 (NCO) cm^{-1} (Found: C, 75.45; H, 5.3; N, 8.3. $C_{21}H_{18}N_2O_2 \cdot 0.25MeOH$ requires C, 75.4; H, 5.65; N, 8.3%).

Methylation of the Lactam (IVd).—A mixture of the lactam (IVd) (8 mg), methyl iodide (10 mg), sodium hydride (10 mg), and anhydrous dioxan (10 ml) was refluxed for 3 h. The solvent was evaporated and the residue was extracted with chloroform. The extract was washed with water and dried. Evaporation of chloroform gave the lactam (IVb) quantitatively, identical with a sample prepared by the reaction of the enamine (II) and acryloyl chloride.

Methylation of the Lactam (IVc).—By the procedure given for (IVb), methylation of the lactam (IVc) (50 mg) with methyl iodide gave the *lactam* (IVa) (45 mg, 87%) as a powder, m.p. 160—162° (from ether–ethanol), $\nu_{max.}$ 1 650 (NCO) cm^{-1} (Found: C, 76.85; H, 6.35; N, 7.6. $C_{23}H_{24}N_2O_2$ requires C, 76.65; H, 6.7; N, 7.75%).

(5β,10β)-2,3-*Dihydro*-6,8-*dimethylergolin*-7-*one* (V).—A solution of the lactam (IVa) (1.5 g) in anhydrous ethanol (100 ml) was hydrogenated over platinum oxide (1 g) at room temperature and 5 atm for 24 h. Filtration and evaporation of the filtrate gave an oil. A mixture of the resulting oil, concentrated hydrochloric acid (20 ml), and acetic acid (18 ml) was refluxed for 8 h. The mixture was cooled, diluted with water (100 ml), and filtered. The filtrate was basified with aqueous ammonia and extracted with chloroform. The extract was washed with water, dried, and evaporated to give a residue which was chromatographed on silica gel to afford the lactam (V) (600 mg, 59%). Trituration with methanol gave a solid which was recrystallised from methanol to afford a pure epimer of the saturated *lactam* (V) as a powder, m.p. 246—248°, $\nu_{max.}$ 3 400 (NH) and 1 620 (NCO) cm^{-1}, δ 7.05 (1 H, t, *J* 7.5 Hz, 13-H), 3.03 (3 H, s, NMe), and 1.20 (3 H, d, *J* 6.5 Hz, CMe) (Found: C, 74.95; H, 7.75; N, 10.85. $C_{16}H_{20}N_2O$ requires C, 74.95; H, 7.85; N, 10.85%).

Costaclavine (VI) *and Epicostaclavine* (VII).—To a solution of the lactam (V) (130 mg) in a mixture of anhydrous ether (20 ml) and tetrahydrofuran (20 ml), lithium aluminium hydride (100 mg) was added in small portions with cooling. After refluxing for 1 h, the solvent was removed. To the residue, ether and water were added carefully to decompose the excess of hydride. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to give an oil. To a solution of the resulting oil in chloroform (10 ml), manganese dioxide (130 mg) was added and stirred at room temperature for 16 h. The mixture was filtered and the solid residue was washed with hot chloroform. The combined chloroform layers were evaporated to give an oil which was purified by preparative t.l.c. to afford costaclavine (VI) (20 mg, 16%) (from methanol), m.p. 183—185° (lit.,[3] 182°), identical (i.r. spectrum and mixed m.p.) with an authentic sample, $\nu_{max.}$ 3 500 (NH), 1 600, 1 460, and 1 440 cm^{-1}. The other amine was *epicostaclavine* (VII) (5 mg, 4%), m.p. 143—145° (from methanol), $\nu_{max.}$ 3 500 (NH), 1 610, and 1 440 cm^{-1} (Found: M^+, 240.163. $C_{16}H_{20}N_2$ requires *M*, 240.163).

Festuclavine (IX).—By the procedure given for (VI), reduction of the lactam (IVa) (200 mg) with lithium aluminium hydride (200 mg) gave a red oil, which was dissolved in anhydrous ether (5 ml). To a mixture of the resulting solution in liquid ammonia (*ca.* 100 ml), sodium (1 g) was added in small portions over 30 min. The

mixture was stirred for a further 1 h before excess of ammonium chloride was added to stop the reaction. Ammonia was evaporated off and the residue was treated with water and ether. The aqueous layer was extracted with ether. The combined ethereal layers were washed with brine, dried, and evaporated to give the amine (VIII) as a black oil. Treated as for (VI), the amine (VIII) with manganese dioxide (100 mg) afforded a crude product, which was purified by preparative t.l.c. to afford festuclavine (IX) (30 mg, 22%) as needles, m.p. 225—228° (lit.,[10] 239—240°) (from methanol), identical (i.r. and mixed m.p.) with an authentic sample, $\nu_{max.}$ 3 500 (NH), 1 600, 1 460, and 1 440 cm^{-1}. Costaclavine (VI) and epicostaclavine (VII) were also isolated by preparative t.l.c. though in low yield.

We thank Dr. S. Yamatodani, Takeda Chem. Ind. Ltd., Osaka, for a gift of clavine alkaloids and for encouragement.

[9/001 *Received*, 2nd *January*, 1979]

REFERENCES

[1] Part 15, I. Ninomiya, O. Yamamoto, T. Kiguchi, and T. Naito, preceding paper.

[2] Preliminary communication, I. Ninomiya and T. Kiguchi, *J.C.S. Chem. Comm.*, 1976, 624.

[3] M. Abe, S. Yamatodani, T. Yamano, and M. Kusumoto, *J. Agric. Chem. Soc. Japan*, 1960, **34**, 360.

[4] S. Yamatodani and M. Abe, *J. Agric. Chem. Soc. Japan*, 1960, **34**, 366.

[5] (*a*) I. Ninomiya, T. Naito, and S. Higuchi, *Chem. Comm.*, 1970, 1662; (*b*) P. W. Hickmott and G. Sheppard, *J. Chem. Soc.* (*C*), 1971, 1358.

[6] I. Ninomiya, T. Naito, S. Higuchi, and T. Mori, *Chem. Comm.*, 1971, 457.

[7] (*a*) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, P. G. Jones, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1956, **78**, 3087; (*b*) J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Medicin. Chem.*, 1974, **17**, 300.

[8] Z. Horii, T. Kurihara, S. Yamamoto, M. C. Hsü, C. Iwata, I. Ninomiya, and Y. Tamura, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1227.

[9] N. J. Bach, H. E. Boaz, E. C. Kornfeld, C. J. Chang, N. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, 1974, **39**, 1272.

[10] M. Abe and S. Yamatodani, *J. Agric. Chem. Soc. Japan*, 1959, **33**, 1031.

[11] Y. Nakahara and T. Niwaguchi, *Tetrahedron*, 1977, **33**, 1591.

[12] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.