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ERGOLINE DERIVATIVES—XIV[1]

SYNTHESIS OF CLAVINE ALKALOIDS

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Abstract—The treatment of methyl lysergate with mercuric acetate in methanol yields, instead of the expected 10 - methoxy - 6 - methyl - ergoline - 8 β - carboxylic acid methyl ester (**2**), 10 - methoxy - 8,9 - didehydro - 6 - methyl - ergoline - 8 - carboxylic acid methyl ester (**3**), whose structure is demonstrated. From **3**, penniclavine (**14**) and isosetoclavine (**15**) were prepared according to Scheme 1.

During our work on 10-alkoxyergoline,†[2,3] the direct, non - photochemical, addition of methanol on 9,10 - didehydro - 6 - methyl - ergoline - 8β - carboxylic acid methyl ester (methyl lysergate, **1**), *via* the solvomercuration - demercuration procedure developed by Brown,[4] was attempted. Mercuric acetate was added to a methanolic solution of **1**, followed by alkaline sodium borohydride but, instead of the expected 10 - methoxy - 6 - methyl - ergoline - 8β - carboxylic acid methyl ester (**2**), a didehydroderivative was isolated.[5] Structure **3** was assigned to this product on the following grounds. The PMR spectrum ($CDCl_3$) shows a broad singlet at δ 7·90‡ (olefinic proton); the UV spectrum shows maxima at 220 and 297 nm indicating that the double bond is not conjugated with the indole ring;[6] catalytic reduction of **3** yields the known[2] 10 - methoxy - 6 - methyl - ergoline - 8α - carboxylic acid methyl ester (**4**) indicating that C_8 is involved in the double bond. Finally the position of the double bond must be as depicted since the isolation of a neutral lactam **5**§ along with **4**, can only be explained by assuming the preliminary formation of **6**, by hydrogenolysis of the *allylic* C_7-N bond, followed by reduction of the double bond and by intramolecular acylation.

The unexpected allylic oxidation observed in the reaction of methyl lysergate with mercuric acetate may be envisaged as the product of a solvolysis of the mercurial acetate group of the intermediate **7** to give **8** with concomitant liberation of Hg°; **8** subsequently yields **3** by loss of a proton. A similar mechanism[7] has been proposed to account for the formation of 4 - hydroxycyclooct - 2 - enone (**9**) from the reaction of cyclooct - 3 - enone (**10**) with mercuric acetate in water.[8]

The generality of the reaction has been verified on a variety of ergot alkaloids.[5] In the present paper we report a facile synthesis of optically active penniclavine (**14**) and isosetoclavine‖ (**15**) from the readily available compound **3**, according to scheme 1 which can be easily adapted to the production of labeled compounds to be used in biosynthetic studies.

10 - Méthoxy - 8,9 - didehydro - 6 - methyl - ergoline - 8 - carboxylic acid methyl ester (**3**) was reduced with LAH to 10 - methoxy - 8,9 - didehydro - 6 - methyl - ergoline - 8 - methanol (**11**) which by short treatment with diluted H_2SO_4 yielded penniclavine (**14**). A minor component (3-5%) was shown to be present by TLC: the same compound was observed when penniclavine itself was treated with dilute H_2SO_4, however the product (isopenniclavine ?) being present in very small amounts could not be isolated in pure form.

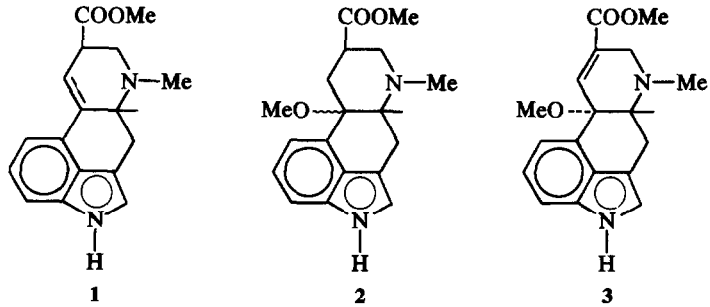
Hydrazinolysis of **3** gave **12** and was converted into the azide by treatment with HNO_2. The azide rearranged into the isocyanate on heating in anhydrous benzene and the isocyanate was hydrolysed, without isolation, to give the unsaturated ketone **13**. Addition of a solution of methylmagnesium bromide to a solution of **13** in anisole yielded isosetoclavine (**15**) and a minor component, probably setoclavine. Equilibration of isosetoclavine in acid solution in the hope of obtaining setoclavine was attempted; however, although the complete disappearance of isosetoclavine was

†Ergoline is the trivial name for (6aR-trans) - 4, 6, 6a, 7, 8, 9, 10, 10a - octahydroindolo [4,3-fg] quinoline.

‡This is a rather low δ value for an olefinic proton, however it has been reported[11] that in the case of 8,9 - didehydro - 6 - methyl - ergoline - 8 - carboxylic acid the H_9 signal has a similar δ value.

§Lactams of analogous structure have been previously[6] obtained by heating dihydrolysergic acid in acetic anhydride at 170°.

‖The preparation of *dl*-isosetoclavine by total synthesis has been recently reported.[9]



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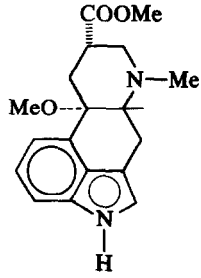

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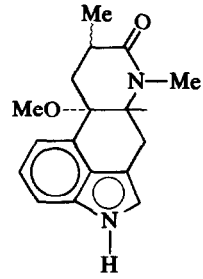

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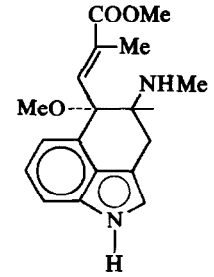

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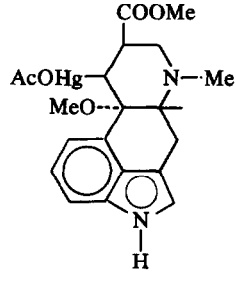

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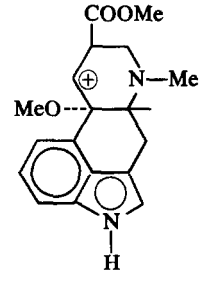

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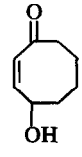

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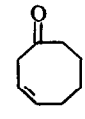

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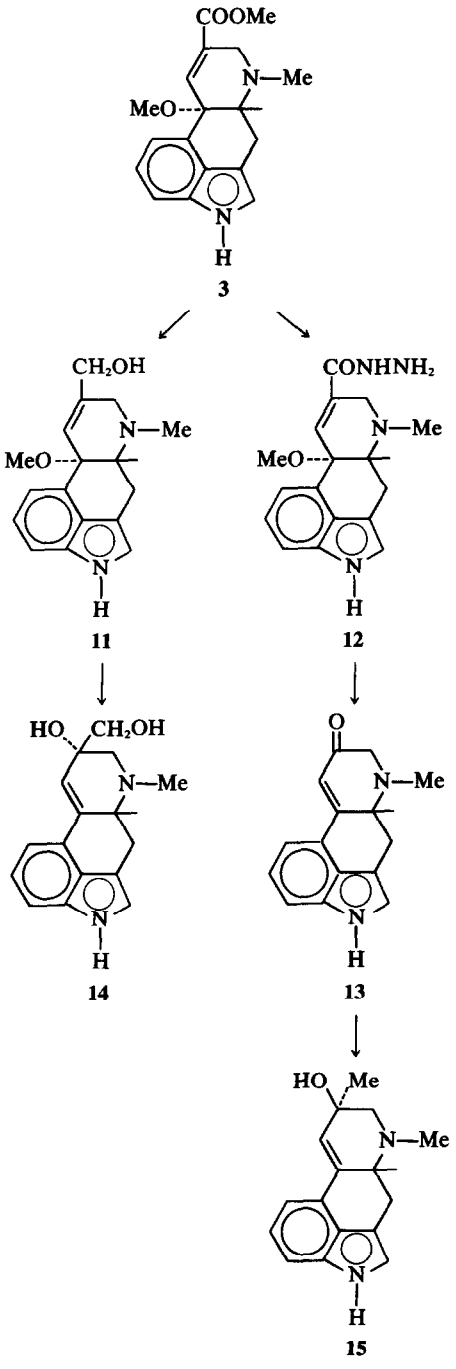
observed within 20 min, a very complex mixture was obtained and no single product could be isolated in a pure state.

EXPERIMENTAL

The PMR spectra were recorded on a Varian A-60 spectrometer, in the indicated solvents, with TMS as internal reference. The IR spectra were recorded on a Perkin-Elmer 457 spectrophotometer as KBr pellets. The optical specific rotation values were determined with a Perkin-Elmer 141 polarimeter. M.ps are uncorrected.

10 - *Methoxy* - 8,9 - *didehydro* - 6 - *methyl* - *ergoline* - 8-*carboxylic acid methyl ester* (**3**). To a soln of methyl lysergate (10 g) in MeOH (150 ml) a soln of $Hg(OAc)_2$ (11·25 g) in MeOH (250 ml) was slowly added under stirring. The soln turned dark-brown and some mercury separated. After 2 hr the soln was cooled to 0°, the pH was adjusted to 9·5 with NaOH and a soln of $NaBH_4$ (1·33 g) in water (10 ml) was added. The mixture was poured on ice-water and extracted with $CHCl_3$. The $CHCl_3$ soln was evaporated and the residue chromatographed on neutral Al_2O_3. On elution with $CHCl_3$ and crystallization from Et_2O, **3** (7·4 g), m.p. 189–190°, $[\alpha]_D^{20} - 270°$ ($C = 1$, $CHCl_3$), was obtained. (Found: C, 69·3; H, 6·5; N, 8·8. $C_{18}H_{20}N_2O_3$ requires: C, 69·2; H, 6·5; N, 9·0%).

Hydrogenation of 10 - *methoxy* - 8,9 - *didehydro* - 6 -



SCHEME 1

methyl - ergoline - 8 - carboxylic acid methyl ester. A solution of **3** (1 g) in AcOH (20 ml) was hydrogenated at room temp and atm press in the presence of PtO_2 catalyst (0·5 g). After evaporation of the solvent, the residue was basified with NH_4OH and extracted with $CHCl_3$. Evaporation of the solvent left a residue that was chromatographed on silicagel plates (1·2 mm; $CHCl_3$/AcOEt 3:2). The two main components were recovered by extraction with MeOH: the slow moving compound was found to be identical (mixed m.p.; IR and $[\alpha]_D$) with 10 - methoxy - 6 - methyl - ergoline - 8α - carboxylic acid methyl ester.[2] The fast moving neutral compound, m.p. 234–236°, showed the following spectroscopic properties: UV, λ max 224, 286, 293 nm; IR (KBr), ν max 3250 (NH), 1620 (N-CO) cm^{-1}; PMR ($CDCl_3$), δ 1·38 (d, J = 7 Hz, 3H, CH_3-CH), 2·95 (s, 3H, CH_3O), 3·10 (s, 3H, CH_3N-CO),* 8·29 (broad s, 1H, NH). On this basis the structure of **5** was assigned to it. (Found; C, 71·7; H, 7·2; N, 9·9; MW (mass) 284. $C_{17}H_{20}N_2O_2$ requires: C, 71·8; H, 7·1; N, 9·8%; MW 284·4).

10 - *Methoxy* - 8,9 - *didehydro* - 6 - *methyl* - *ergoline* - 8 - *methanol* (**11**). To a suspension of LAH_4 (10 g) in THF (250 ml) a soln of **3** (10 g) in THF (250 ml) was slowly added at 5°. After 5 hr water (50 ml) was cautiously added, the soln filtered and THF evaporated *in vacuo*. The residue was taken up in $CHCl_3$ with the help of some MeOH, the soln was washed with water and evaporated to dryness. The residue was crystallized from acetone to give **11** (6·5 g), m.p. 219–221°, $[\alpha]_D^{20} - 202°$ ($c = 1$, pyridine). (Found: C, 71·5; H, 7·2; N, 9·7. $C_{17}H_{20}N_2O_2$ requires: C, 71·8; H, 7·1; N, 9·8%); PMR spectrum (DMSO-d_6): δ 2·28 (s, 3H, N-CH_3), 2·95 (s, 3H, CH_3O), 3·96 (broad, 2H, $C_{17}H_2$), 4·85 (t, 1H, OH), 6·56 (s, 1H, C_9H).

Penniclavine (**14**). A soln of **11** (1 g) in water (25 ml) and H_2SO_4 (5 ml) was kept at room temp for 1 hr, then cooled and basified with NH_4OH. The soln was extracted with $CHCl_3$: evaporation of the solvent left a residue that was crystallized from acetone to give **14** (0·7 g), m.p. 224–228°, $[\alpha]_D^{20} + 150°$ ($c = 1$, pyridine) (lit[10] m.p. 222–225°; $[\alpha]_D^{20} + 153°$). IR spectrum: identical with the reported[10] spectrum of penniclavine.

10 - *Methoxy* - 8,9 - *didehydro* - 6 - *methyl* - *ergoline* - 8 - *carboxylic acid hydrazide* (**12**). A soln of **3** (5 g) in MeOH (25 ml) and hydrazine hydrate (100 ml) was kept at 60° for 30 min: after evaporation of the solvent the residue was crystallized from EtOH to give **12** (3·1 g), m.p. 220–222°; $[\alpha]_D^{20} - 277°$ ($c = 1$, pyridine). (Found C, 65·1; H, 6·5; N, 17·8. $C_{17}H_{20}N_4O_2$ requires: C, 65·3; H, 6·5; N, 17·9%).

9,10 - *Didehydro* - 6 - *methyl* - *ergolin* - 8 - *one* (**13**). To a soln of **12** (3 g) in 0·2N HCl (120 ml), $NaNO_2$ (0·66 g) in water (30 ml) was added at 0°. After 30 min the soln was basified with $NaHCO_3$ and extracted with Et_2O. After evaporation of the solvent the residue was taken up in benzene (200 ml) and refluxed for 2 hr. After evaporation of the solvent the residue was dissolved in 0·2N HCl (200 ml) and kept at room temp for 1 hr. The soln was basified with $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent left a residue that was crystallized from acetone to give **13** (2 g), m.p. 164–166°; $[\alpha]_D^{20} + 703°$ ($c = 1$, MeOH); λ_{max} 262, 392 nm (MeOH). (Found: C, 75·5; H, 5·9; 0, 6·9. $C_{15}H_{14}N_2O$ requires: C, 75·6; H, 6·0; 0, 6·7%).

Isosetoclavine (**15**). To a soln of MeMgBr prepared from 4·1 g of Mg in Et_2O (100 ml), **13** (1·6 g) in anisole (100 ml) was added. The mixture was left overnight at room temp, then a saturated soln of NH_4Cl (50 ml) was added. The organic layer was separated and the water soln repeatedly extracted with $CHCl_3$. The organic extracts were evaporated *in vacuo* and the residue was crystallized from MeOH to give **15** (0·9 g), m.p. 234–236°,

*The chemical shift of the MeN group in all basic ergolines so far examined was found to be around 2·4 δ (*cf* ref 3).

$[\alpha]_D^{20} + 102°$ ($c = 1$, pyridine) (lit.[10] m.p. 234–237°; $[\alpha]_D^{20} + 107°$). IR spectrum: identical with the reported[10] spectrum of isosetoclavine.

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