An Improved Synthesis of (±)-Lycoramine

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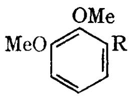
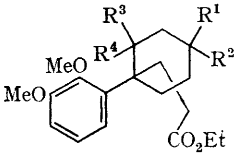
DURING our synthetic studies of lycoramine,[1,2] we encountered difficulty at one step.[3] Although the problem has recently been solved, attention was turned at that time to an alternative method of synthesis. We report here a new route to lycoramine, starting from 2,3-dimethoxybenzaldehyde, through a sequence of 18 steps in a far better overall yield (0·67%) than that of the initial pathway.

The first step in the synthesis involved condensation of 2,3-dimethoxybenzaldehyde with nitroethane, giving in 72% yield the benzalnitroethane (I) which on reduction with iron in hydrochloric acid afforded in 62% yield the phenylacetone (II). Michael condensation of (II) with acrylonitrile gave in 65% yield the pimelonitrile (III) which was saponified in an alkaline solution and esterified in ethanol in the presence of toluene-*p*-sulphonic acid to afford almost quantitative yield of the ethyl pimelate (IV). Cyclisation of this keto-ester (IV) with sodium ethoxide in ethanol gave in 82% yield the diketone (V), m.p. 131—132°. Selective acetalisation of this with an excess of ethyl methyl ketone ethylene-ketal in the presence of boron trifluoride gave in 95% yield the monoketal (VI) which was treated with lithium aluminium hydride in tetrahydrofuran and then with oxalic acid in boiling aqueous ethanol to furnish in 74% yield the perhydrobenzopyran (VII), m.p. 125—126°. Treatment of (VII) with constant-boiling hydriodic acid for 5 min. gave in 58% yield the hexahydrodibenzofuran (VIII), m.p. 140—141°, as a result of cleavage of the pyran ring along with the methoxy-groups and subsequent recyclisation. The spectral data were consistent with this structure (VIII). Methylation of the hydroxy-group in (VIII) with methyl iodide and potassium carbonate in acetone proceeded quantitatively, and subsequent treatment of the resulting (IX) with silver acetate in boiling acetonitrile gave in 80% yield the acetoxy-compound (X), which gave on hydrolysis with hydrochloric acid in 88% yield the hydroxy-ketone (XI). Chromic acid oxidation of (XI) in acetone containing sulphuric acid afforded in 72% yield the keto-acid (XII), m.p. 140·5—141·5° which was treated with sodium borohydride to give in 80% yield the hydroxy-acid (XIII).

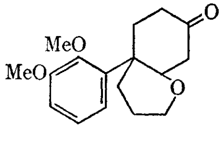
Acetylation of the hydroxy-group in (XIII) followed by cyclisation of the carboxylic acid (XIV) with stannic chloride in benzene through its acid chloride gave in 91% yield the tetralone (XV), m.p. 125—126·5°. The Schmidt reaction on the tetralone (XV) using sodium azide in trichloroacetic acid gave a mixture of two isomeric lactams which were separated chromatographically. One compound, m.p. 207·5—208°, was obtained in 38% yield, and assigned the structure (XVI) based on the spectral properties. The other compound, m.p. 198—201°, obtained in 34% yield, was shown to have the structure



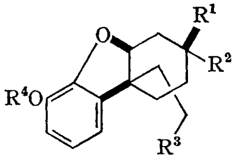
(I) R=CH:C(NO_2)Me
(II) R=CH_2·COMe
(III) R=C[CH_2·CH_2CN]$_2$ with CO·Me on C
(IV) R=C[CH_2·CH_2·CO_2Et]$_2$ with CO·Me on C



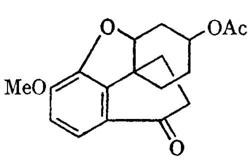
(V) $R^1R^2=R^3R^4=O$
(VI) $R^1R^2=\begin{matrix}O\\O\end{matrix}\Big]$, $R^3R^4=O$



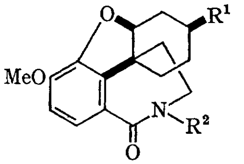
(VII)



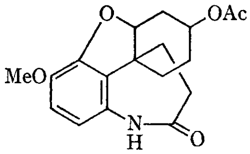
(VIII) R^1R^2=O, $R^3=CH_2I$, R^4=H
(IX) R^1R^2=O, $R^3=CH_2I$, R^4=Me
(X) R^1R^2=O, $R^3=CH_2OAc$, R^4=Me
(XI) R^1R^2=O, $R^3=CH_2OH$, R^4=Me
(XII) R^1R^2=O, $R^3=CO_2H$, R^4=Me
(XIII) R^1=OH, R^2=H, $R^3=CO_2H$, R^4=Me (XIV) R^1=OAc, R^2=H, $R^3=CO_2H$, R^4=Me



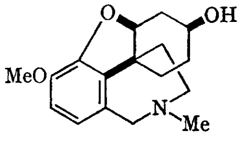
(XV)



(XVI) R^1=OAc, R^2=H
(XVIII) R^1=OAc, R^2=Me



(XVII)



(XIX)

(XVII). The desired lactam (XVI) was *N*-methylated by heating in toluene with methyl iodide and sodium hydride and the *N*-methyl derivative (XVIII) thus obtained in 65% yield had m.p. 229—231° and was shown to be identical with (±)-oxolycoramine acetate (XVIII) prepared from (±)-lycoramine by permanganate oxidation followed by acetylation. Treatment of (±)-oxolycoramine acetate (XVIII) with lithium aluminium hydride in tetrahydrofuran gave in 78% yield (±)-lycoramine (XIX), m.p. 98—99°, thus accomplishing a new total synthesis of this alkaloid.

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[2] D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806.
[3] N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, S. Uyeo, and A. Yoshitake. Paper presented at the 11th National Symposium on the Chemistry of Natural Products held in Kyoto, Japan, Oct. 9—11, 1967.