Biotransformation of (+)-Reticuline in Rat

Reticuline (I) is well known as the most important precursor of the opium alkaloids, such as protoberberine, morphine, aporphine, benzophenanthridine, and phthalidioisoquinoline alkaloid in plant.1) It was of interest for us to investigate the biotransformation of reticuline in the living animal. Now we wish to report a formation of coreximine (II), which we believe first observation, from reticuline in rats.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{HO} & \quad \text{HO} \\
\text{NMe} & \quad \text{NMe} \\
\text{I} & \\
\text{II}
\end{align*}
\]

A solution of (+)-reticuline in propylene glycol was injected intraperioneally (200 mg/kg) into five female rats, and the urine was collected in bottle containing a few drops of toluene for 4 days after the injection. The pooled urine was adjusted to pH 5 with dil. H₂SO₄ and then to pH 4.5 with 0.1 mole acetate buffer (10 ml/100 ml of urine) and incubated with β-glucuronidase at 37° for 5 days.2) The hydrolyzate was adjusted to pH 1 with dil. HCl, and the resulting solution was washed with ether, then made basic with NH₄OH and extracted with CHCl₃. The basic fraction was separated by preparative thick-layer chromatography on silica gel (Wakogel B-5) in CHCl₃-MeOH (10:1) to yield 6 mg of reticuline and 1 mg of a protoberberine, the latter thin-layer chromatography behavior of which in two solvent system [CHCl₃-MeOH (10:1), benzene-AcOEt-MeOH (5:4:1)] was identical with that of coreximine. The mass spectrum showed characteristic fragmentation of protoberberine, m/e 327 (M⁺), 326, 178, and 150. The base was converted with hexamethyldisilazane and trimethylchlorosilane in pyridine to trimethylsilyl ether (TMSE) and analyzed by gas liquid partition chromatography (GLPC). The GLPC behavior of TMSE on 1.5% OV-1 (1.5 m) at 235° (detection and injection port temperature at 260°) with a nitrogen flow rate of 60 ml/min, \( R_e = 2.13, \) was identical with that of coreximine-TMSE. In this experiment, formation of sinoacutine, pallidine, isoboldine, and scoulerine was not observed.

Acknowledgement We are indebted to Professor T. Nambara, Dr. K. Shimada, Mr. Y.B. Bae and Mr. M. Nokubo in this pharmaceutical Institute, for kind help with the biological experiments and gas chromatography.

3) GLPC data were obtained with a Shimazu Model GC-IC gas chromatography equipped with hydrogen ionization detector. Re-retention time is relative to cholestanol.
Synthesis of 3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-phenyl-1H-dibenzo[\(b,e\)][1,4]diazepin-1-one, a New Tricyclic System

Recent development of seven-membered ring compound as psychopharmaceutical agents including benzodiazepine\(^1\)\(^-\)\(^2\) and dibenzodiazepine\(^3\) led us to attempt the synthesis of a series of linearly fused tricyclic compounds in which one of the six-membered rings is partly saturated. In the present paper we wish to report a simple and convenient synthesis of the title compound (II), a new 6-7-6 ring system.

\[
\begin{array}{c}
\text{I} \\
N \quad \text{NH}_2 \\
\text{NH} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{II} \\
N \quad \text{H} \\
\text{NH} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{III} \\
N = \text{CH} \\
\text{O} \\
\end{array}
\]

\[R=\text{H},\text{CH}_3,\text{C}_2\text{H}_5,\text{C}_6\text{H}_5,\text{C}_4\text{H}_4\text{Cl (p)}\]

Our method consists of interaction of an aldehyde with 3-(\(\alpha\)-aminoanilino)-5,5-dimethyl-2-cyclohexen-1-one (I) and the cyclization is brought about by loss of water. I is readily available by condensation of \(\alpha\)-phenylenediamine with dimesdone.

It is remarkable that the reaction is complete by simply allowing the reactants at room temperature with a small amount of acid catalyst such as acetic acid and hydrochloric acid. The high reactivity of I with an aldehyde can be attributable to enaminostructure involved in I in which \(\alpha\)-position is particularly reactive to electrophilic reagents.\(^4\)\(^-\)\(^7\)

Apparently the ring closure, I \(\rightarrow\) II, is a variation of Mannich reaction. To our knowledge this is the first example of formation of diazepine ring system by Mannich type cyclization.

The structure II (R=\(\text{C}_6\text{H}_5\)) is supported by infrared (IR) and nuclear magnetic resonance (NMR) spectra, the other possible structure III (R=\(\text{C}_4\text{H}_4\text{Cl}\)) being ruled out. The IR spectrum (CHCl\(_3\)) showed absorptions at 3412, 3340, 1610, 1587, 1515 cm\(^{-1}\) (vinyllogous amide)\(^8\) and