# Studies on the Syntheses of Heterocyclic Compounds. Part DLXXXII (1). Synthesis of Benzo[*a*]quinolizine Derivatives and Pyrrolo[2,1-*a*]isoquinoline Derivatives by Phenolic Cyclization.

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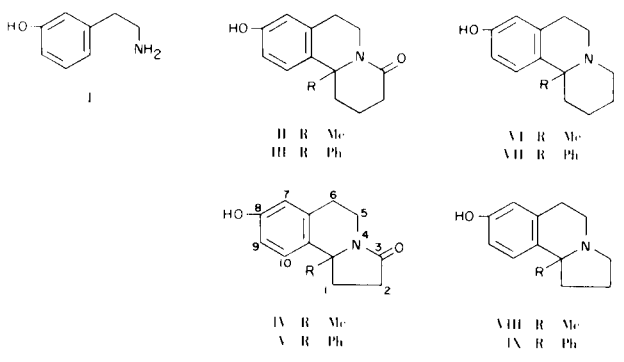
Phenolic cyclization of 3-hydroxyphenethylamine with acylbutyric acid and acylpropionic acid afforded the lactam of the corresponding benzo[*a*]quinolizine and pyrrolo[2,1-*a*]isoquinoline derivatives, which were reduced with lithium aluminum hydride to give the benzo[*a*]quinolizine and pyrrolo[2,1-*a*]isoquinoline derivatives, respectively. The configurations of acetyl derivatives of these products were determined.

It has been reported that the treatment of 3-hydroxyphenethylamine I with several carbonyl compounds without acidic catalysts gave 1,1-disubstituted 1,2,3,4-tetrahydro-6-hydroxyisoquinoline derivatives and the cyclization proceeded preferentially at the *para* position to the phenolic hydroxy group (3). Also, one of our authors has reported that the treatment of 2-amino-1-(3-hydroxyphenyl)-ethanol with levulinic acid gave 1,2,3,5,6,10b-hexahydro-8-hydroxy-10b-methylpyrrolo[2,1-*a*]isoquinoline-3-one (4). We now wish to report an extension of these studies.

The reaction of the preceding amine I with levulinic acid, 3-benzoylpropionic acid, 4-acetobutyric acid and 4-benzoylbutyric acid under fusion at 150-200° or reflux using isopropanol as solvent gave the lactams II-V, the reduction of which with lithium aluminum hydride gave benzo[*a*]quinolizine VI and VII and pyrrolo[2,1-*a*]isoquinoline derivatives VIII and IX.

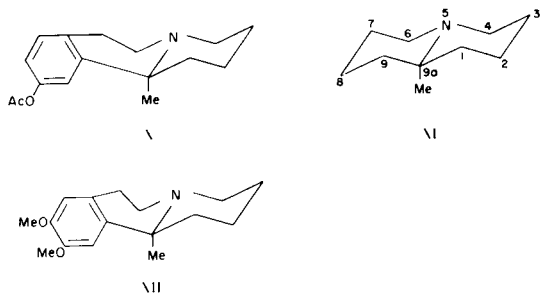
Chart 1




1,2,3,5,6,10b-Hexahydro-8-hydroxy-10b-methylpyrrolo[2,1-*a*]isoquinoline-3-one (IV) obtained from the cyclization of amine I with levulinic acid showed a carbonyl absorption at 1660 $cm^{-1}$ in the ir spectrum and absorption maximum at 279 nm in the uv spectrum, whereas the starting amine I showed an absorption maximum at 274 nm (3d). The compound IV showed 10b-methyl as a singlet at 1.4 ppm, $C_9$-aromatic proton as a doublet of doublet ($J$ = 9.0 Hz, $J$ = 2.5 Hz) centered at 6.60 ppm, and $C_{10}$-aromatic proton as a doublet ($J$ = 9.0 Hz) centered at 7.01 ppm in the nmr spectrum. These data showed that the cyclization proceeded preferentially at the *para* position to the hydroxy group.

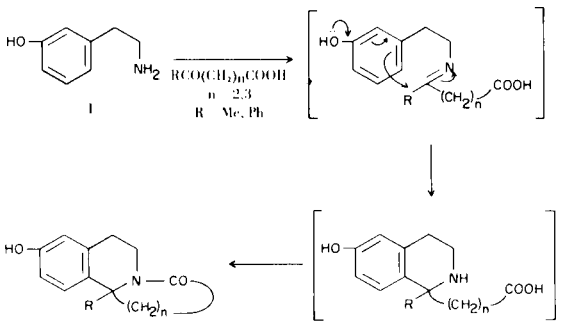
After reduction of compound IV with lithium aluminum hydride in dioxane, pyrrolo[2,1-*a*]isoquinoline derivative VIII was obtained as its hydrochloride. Compound VIII showed an absorption maximum at 279 nm in the uv spectrum and no absorption at 1660 $cm^{-1}$ due to carbonyl group was observed in the ir spectrum. Bohlmann

Chart 2




has reported that the configuration of 9a-methylquinolizidine (XI) is *trans* because the presence of Bohlmann bands in the ir spectrum (5). Terzyan also reported that the configuration of 1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-

Chart 3



11b-methyl-2*H*-benzo[*a*]quinolizine (XII) is *trans* because of the appearance of Bohlmann bands (6). Accordingly, 9-acetoxy-1,3,4,6,7,11b-hexahydro-11b-methyl-2*H*-benzo[*a*]-quinolizine (X) was assumed to be *trans* since the ir spectra as a solution in carbon tetrachloride and as a neat showed an absorption between 2750 $cm^{-1}$ and 2085 $cm^{-1}$. But the Bohlmann bands of the other compounds is not clear, so its configuration is under examination.

The mechanism of this reaction is considered as follows. The Schiff's base is firstly formed from the reaction of amine I with ketocarboxylic acid and then the tetrahydroisoquinoline derivative, which formed by the cyclization at the *para* position to phenolic hydroxy group, would be transformed to the lactam by the condensation of amine with carboxylic acid.

## EXPERIMENTAL

### The Reaction of 3-Hydroxyphenethylamine with Ketocarboxylic Acids.

After the reaction of amine I with ketocarboxylic acid derivative under the conditions as shown in Table I, the solvent was evaporated and the residue was dissolved in ethanol and chloroform. The resulting solution was washed with 28% ammonia and water. After evaporation of the solvent, the product was recrystallized from appropriate solvents. Thus compounds II, III, IV, and V were obtained.

### The Reduction of Lactam.

Compounds II, III, IV, and V were reduced with lithium aluminum hydride in dioxane under reflux for 2 hours according to the conditions as shown in Table II. The reaction mixture was worked up as usual. Thus the hydrochloride of compounds VI, VII, VIII, and IX was obtained.

### *O*-Acetyl-1,3,4,6,7,11b-hexahydro-11b-methyl-2*H*-benzo[*a*]-quinolizine (X).

A solution of 200 mg. of compound VI in 1 ml. of acetic anhydride was refluxed for 2 hours and the mixture was dissolved in ether. The ethereal solution was washed with 10% ammonia and water, dried over sodium sulfate and evaporated to give 200 mg. (83%) of X as a colorless oil, $\nu$ max (liquid) $cm^{-1}$: 1760 (C=O), 2750 ~ 2805 (Bohlmann bands).

TABLE I

The Reaction of 3-Hydroxyphenethylamine (I) with Ketocarboxylic Acids

| Compound No. | Starting materials | | Solvent | Temp. °C | Time hours | Products | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Ketocarboxylic acid (g) | Amine (I) (g) | | | | Yield g (%) | Appearance (recrystallization solvents) M.p. °C | Ir $\nu$ max KBr ($cm^{-1}$)(C=O) | Uv $\lambda$ max (ethanol) (nm) |
| II | 4-Acetobutyric acid (1.00) | 1.00 | none | 200 | 1 | 0.87 (51) | colorless granules (2-propanol) 185-186 | 1600 | 279 |
| III | 4-Benzoylbutyric acid (0.38) | 0.27 | none | 200 | 1 | 0.41 (71) | colorless granules (2-propanol) 263-265 | 1600 | 278 |
| IV | Levulinic acid (0.40) | 0.40 | 2-propanol | reflux | 5 | 0.24 (38) | colorless granules (2-propanol) 212-213 | 1660 | 279 |
| | | | none | 200 | 1 | 0.37 (59) | | | |
| V | 3-Benzoylpropionic acid (0.41) | 0.41 | none | 200 | 1 | 0.48 (57) | colorless granules (2-propanol) 237-239 | 1650 | 279 |

TABLE II

Reduction of Lactams with Lithium Aluminum Hydride

| Compound No. | Lactam No. (g.) | Yield g. (%) | Appearance | Recrystallization solvent | M.p. °C | Uv λ max (ethanol) (nm) |
|---|---|---|---|---|---|---|
| VI | (II) (0.50) | 0.37 (71) | colorless powder | 2-propanol | 230 dec. | 279 |
| VII | (III) (0.20) | 0.14 (65) | colorless needles | ethanol | 270 | 280 |
| VIII | (IV) (0.20) | 0.16 (72) | colorless needles | 2-propanol | 188 dec. | 279 |
| IX | (V) (0.20) | 0.17 (79) | colorless powder | ethanol | 244-246 | 280 |

TABLE III

Microanalysis

| Compound No. | Formula | Calcd. (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|
| II | $C_{14}H_{17}O_2N$ | 72.70 | 7.41 | 6.06 | 72.70 | 7.24 | 6.07 |
| III | $C_{19}H_{19}O_2N$ | 77.79 | 6.53 | 4.77 | 77.55 | 6.18 | 4.71 |
| IV | $C_{13}H_{15}O_2N$ | 71.86 | 6.96 | 6.45 | 71.81 | 7.03 | 6.48 |
| V | $C_{18}H_{17}O_2N$ | 77.39 | 6.13 | 5.01 | 76.93 | 6.33 | 4.65 |
| VI | $C_{14}H_{19}ON\cdot HCl$ | 66.26 | 7.94 | 5.52 | 66.24 | 8.10 | 5.20 |
| VII | $C_{19}H_{21}ON\cdot HCl$ | | | 4.44 | | | 4.32 |
| VIII | $C_{13}H_{17}ON\cdot HCl$ | 65.13 | 7.57 | 5.84 | 65.17 | 7.86 | 5.45 |
| IX | $C_{18}H_{19}ON\cdot HCl$ | 71.63 | 6.68 | 4.64 | 71.23 | 6.80 | 4.63 |

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(2) Communication concerning this paper should be directed to Professor Tetsuji Kametani.

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