23. *Synthesis of Some 1,2-Polymethylene-tetrahydro-isoquinolines.*¹⁾

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From physiological view-point one of the present authors (Sugasawa) is interested in synthesizing condensed nitrogen-ring-compounds and has hitherto published several papers dealing with the synthesis of some pyridocolinederivatives with his co-workers.²⁾ The present communication is concerned with the synthesis of some 1,2-polymethylene-1,2,3,4-tetrahydro-isoquinolines having the general formula (I) ($R=R'=OCH_3$ or $R-R'=O-CH_2-O$, $R''=H$ or CH_3 , $n=2, 3$ or 4).

Having investigated the chemistry of ipecacuanha-alcaloids, Pyman and his co-workers³⁾ came to the conclusion that the chemical behaviours of emetine, the most important ipecacuanha-alcaloid, best accord with the formula (II) and a few years later Child and Pyman⁴⁾ synthesized some compounds related to pyridocoline-moiety of emetine, therefore 1,2-polymethylene-isoquinolines, which, however, did not show any interesting physiological activity against their expectation.

Our present investigation covers nearly the same ground, but the method of preparation is quite different from theirs, intending to find some approach to the important alcaloid emetine.⁵⁾

When acid imides reduced electrolytically according to Tafel, only one of the two carbonyl-groups is generally converted into methylene-group forming the corresponding lactams.⁶⁾ Therefore, if the original acid imide is appropriately chosen, the reduction product, the lactam, would give 1,2-polymethylene-isoquinolinium-salts on ring-closure, and this was really the case.

1) XVII. Communication upon "Studies on the Synthesis of Nitrogen-Ring-Compounds" by Sugasawa.

2) Sugasawa: J. Pharm. Soc. Japan **57** (1937), 296.

Sugasawa and Kakemi: Proc. **14** (1938), 214; Ber. **71** (1938), 1860.

Sugasawa and Sugimoto: Proc. **15** (1939), 49.

Sugasawa and Kakemi: Proc. **15** (1939), 52.

3) Brindley and Pyman: Soc. **1927**, 1067 and previous papers.

4) Soc. **1931**, 36.

5) cf. Sugasawa and Sugimoto: loc. cit.

6) cf. Houben: Methoden der Org. Chemie II. Band 281.

Sakurai: Bull. Chem. Soc. Japan, **5** (1930), 184.

cf. Sugasawa and Tsuda: J. Pharm. Soc. Japan. **55** (1935), 194.

For our present work such acid imides (VI: $n=2$ or 3) were prepared as follows. Substituted β -phenylethylamines (III) and succinic- or glutaricanhydride (IV: $n=2$ or 3) were heated in benzene solution for about one hour, and the residue, which was obtained after evaporating the solvent and consisted mostly of the intermediate amido-acids (V),¹⁾ was again heated for another hour with an excess of acetic anhydride added with a drop of pyridine.

Succinimides (VI: $n=2$) thus obtained yielded the corresponding lactams (VII: $n=2$) in fairly good yield, when they were reduced electrolytically in acetic-sulphuric acid solution, whereas in case of glutarimides (VI: $n=3$) some by-products, probably reduction products of various stages, were produced together with the desired lactams (VII: $n=3$).

The behaviour of adipic anhydride towards β -phenylethylamines is quite different: adipic-di- β -phenylethylamides (IX) are the main products and the formation of the imides is scarcely recognized. The direct preparation of lactams (VII: $n=4$) by condensing potassium ϵ -amino- n -caproic lactam (X) with β -phenylethylbromides was then attempted, which expectation was, however, only partially realized.

When potassium ϵ -amino- n -caproic lactam, prepared by heating the lactam and powdered potassium in dry xylene, was treated with β -piperonylethyl bromide (XI: $R''=H$) in boiling xylene solution in the presence of a little copper powder, the condensation product, ϵ -N- β -piperonylethylamino- n -caproic lactam (VII: $R-R'=O-CH_2-O$, $R''=H$, $n=4$) was obtained as brown viscous syrup in about 35 % yield, while, in case safrolhydrobromide (XI: $R''=CH_3$) was used, isosafrole was the main reaction product and the yield of the desired lactam (VII: $R-R'=O-CH_2-O$, $R''=CH_3$, $n=4$) was too poor for our ultimate purpose.

The various lactams thus prepared underwent uniformly the action of phosphoryl chloride in boiling dry toluene solution forming substituted 1,2-polymethylene-3,4-dihydro-isoquinolinium-salts (VIII), which on catalytic hydrogenation readily gave the corresponding tertiary bases (I).

1) The formation of by-products of di-amide-typus (compare formula IX) was recognized in this case too, but in far less quantity than in the case when adipic anhydride was condensed with amines (see below).

The properties of ultimate products and intermediates, so far they or their derivatives obtained crystalline and characterized, are briefly described below in groups of $n=2, 3$ or 4 .

I. Group: 1, 2-Polymethylene-1, 2, 3, 4-tetrahydroisoquinolines (I: $n=2$).

1. Case: $R=R'=OCH_3$, $R''=H$.

i) N- β -Veratrylethyl-succinamido-acid (V): Colourless leaflets from benzene, m. p. 108.5° . ($C_{14}H_{19}O_5N$ requires C 59.8, H 6.8; Found C 60.1, H 6.9).

ii) N- β -Veratrylethylsuccinimide (VI): Colourless needles from benzene-petrolether, m. p. 130° .¹⁾ ($C_{14}H_{17}O_4N$ requires C 63.9, H 6.5; Found C 63.6, H 6.4).

iii) 1, 2-Trimethylene-6, 7-dimethoxy-3, 4-dihydroisoquinolinium picrate (VIII: $X=O-C_6H_2(NO_2)_3$): Yellow needles from alcohol, d. p. $193-194^\circ$.²⁾ ($C_{20}H_{20}O_9N_4$ requires C 52.1, H 4.4; Found C 51.8, H 4.7).

iv) 1, 2-Trimethylene-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (I): Colourless rhombic pillars from petrolether, m. p. $87-88^\circ$.³⁾

Picrate: Yellow minute needles from alcohol, m. p. 186° .⁴⁾

2. Case: $R-R'=O-CH_2-O$, $R''=CH_3$.

i) N- α -Methyl- β -piperonylethylsuccinamido-acid (V): Colourless needles from alcohol, m. p. 134.5° (not analysed).

ii) N- α -Methyl- β -piperonylethylsuccinimide (VI): Colourless plates from benzene-petrolether, m. p. 80° . ($C_{14}H_{15}O_4N$ requires C 64.4, H 5.7, N 5.4; Found C 64.1, H 5.8, N 5.7).

iii) 1, 2-Trimethylene-3-methyl-6, 7-methylenedioxy-3, 4-dihydroisoquinolinium iodide (VIII: $X=I$): Yellow rhombic pillars from water faintly acidified with hydroiodic acid, d. p. 245° . ($C_{14}H_{16}O_2NI$ requires C 47.1, H 4.5, N 3.9; Found C 47.3, H 4.6, N 3.9).

iv) 1, 2-Trimethylene-3-methyl-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinoline (I): Colourless minute needles from dilute methanol, m. p. 75.5° . ($C_{14}H_{17}O_2N$ requires C 72.7, H 7.4, N 6.1; Found C 72.8, H 7.5, N 6.5).

Hydrochloride: Colourless needles, d. p. 234° .

II. Group: 1, 2-Tetramethylene-1, 2, 3, 4-tetrahydroisoquinolines (I: $n=3$).

1. Case: $R=R'=OCH_3$, $R''=H$.

i) N- β -Veratrylethylglutarimide (VI): Colourless needles from benzene, m. p. $113-114^\circ$. ($C_{16}H_{19}O_4N$ requires C 65.0, H 6.8, N 5.1; Found C 65.0, H 7.0, N 5.2).

1) m. p. 129° according to Child and Pyman: Soc. **1929**, 2010.

2) d. p. $200-201^\circ$ according to Child and Pyman: Soc. **1931**, 36.

3) m. p. $88-89^\circ$ " " " "

4) m. p. 187° " " " "

ii) 1, 2-Tetramethylene-6, 7-dimethoxy-3, 4-dihydroisoquinolinium picrate (VIII: $X = O-C_6H_2(NO_2)_3$): Yellow plates from alcohol, d. p. 179–180°. ¹⁾ ($C_{21}H_{22}O_9N_4$ requires C 53.2, H 4.7, N 11.8; Found C 52.5, H 4.4, N 11.7).

iii) 1, 2-Tetramethylene-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline²⁾ (I): The free base is brown viscous syrup and the perchlorate is only derivative obtained crystalline so far investigated, which separates in colourless grains of m. p. 185° from water. ($C_{15}H_{21}O_2N \cdot HClO_4$ requires C 52.3, H 6.3, N 4.0; Found C 52.1, H 6.2, N 4.1).

2. Case: $R-R' = O-CH_2-O$, $R'' = CH_3$.

i) N- α -Methyl- β -piperonylethylglutaramido-acid (V): Colourless needles from much benzene, m. p. 95.5°. ($C_{15}H_{19}O_6N$ requires C 61.4, H 6.5; Found C 61.8, H 6.5).

ii) 1, 2-Tetramethylene-3-methyl-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinoline (I): The free base is light brown viscous syrup and was characterized as crystalline perchlorate, which forms needles from water, m. p. 183–183.5° after being dried at 130° for 20 hours in vac. ($C_{15}H_{19}O_2N \cdot HClO_4$ requires C 51.7, H 6.1, N 4.0; Found C 52.1, H 5.8, N 4.1).

III. Group: 1, 2-Pentamethylene-Derivatives (I: $n = 4$).

i) 1, 2-Pentamethylene-6, 7-methylenedioxy-1, 2, 3, 4-tetrahydroisoquinoline (I: $R-R' = O-CH_2-O$, $R'' = H$): Free base: Brown viscous syrup.

Picrate: Yellow needles from dilute alcohol, d. p. 154°. ($C_{21}H_{22}O_9N_4$ requires C 53.2, H 4.6; Found C 52.8, H 4.8).

ii) 1, 2-Pentamethylene-3-methyl-6, 7-methylenedioxy-3, 4-dihydroisoquinolinium iodide (VIII: $R-R' = O-CH_2-O$, $R'' = CH_3$, $X = I$): Pale yellow needles from alcohol-ether, d. p. 238–239°. ($C_{16}H_{20}O_2NI$ requires C 49.7, H 5.4; C 50.1, H 5.5).

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1) D. p. of the picrate recorded by Child and Pyman is 185–186°: Soc. **1931**, 46.

2) Child and Pyman describe the free base as nodular crystals of m. p. 59–60°, which gives crystalline hydrochloride (m. p. 235–237°), picrate (d. p. 172–174°) and crystalline α - and β -methiodides (m. p. 244–245° and 228° respectively). The property of our base is so different from that of these authors' and further considerations are necessary about this point.