25. Studies on the Synthesis of Dibenzoindolizine-Derivatives (I).

A Synthesis of 4',5':4'',5''-Tetramethoxy-3,8,4,7-tetrahydro-(1',2':1,2; 1'',2'':5,6-dibenzoindolizine)).*

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(Comm. by Y. ASAHINA, M.I.A., April 12, 1941.)

For some years Sugasawa and his collaborators¹⁾ have been engaged in synthesizing dibenzopyridocoline-derivatives and they so far succeeded in preparing four hitherto unknown or not exactly known compounds out of seven theoretically possible dibenzopyridocolines, of which one belongs to the well-known berberine-type of alkaloids. Since it seemed to us not without interest to compare the properties of these dibenzopyridocolines with those of the corresponding dibenzoindolizines, we commenced the synthetical work in this field.

Indolizine, indolizidine and their derivatives have been the subjects of investigations by different authors, but not much is known about dibenzoindolizines. As shown in the following diagramm there are seven theoretically possible skeletons (A-G) in this type of compounds, none of which has yet been found in natural alkaloids²⁾.

Nearly a decade ago in their attempt to dehydrogenate benzyl-isoquinoline-derivative into aporphine, Robinson and Sugasawa³⁾ treated laudanosoline(I)-salt with chloranil in alcoholic solution. Their expectation was not realized and as they found a new dibenzoindolizine having

*) S. Sugasawa: XXIV. Comm. upon "Studies on the Synthesis of Nitrogen-Ring-Compounds."

The nomenclature "Indolizine" will be used instead of "Pyrrocoline" throughout this series of work.

1) Proc. **14** (1938), 214; Ber. **71** (1938), 1860. Proc. **15** (1939), 52; Ber. **72** (1939), 980. Proc. **15** (1939), 223; Ber. **73** (1940), 782. Proc. **16** (1940), 473; Ber. **74** (1941), 455.

2) Recently H. Kondo and H. Katsura elucidated the constitution of lycorine to be a hydroxy-derivative of benzoindolizine. cf. Ber. **73** (1940), 1424 and previous papers.

3) Soc. **1932**, 789. compare also Schöpf, Thierfelder: Ann. **497** (1932), 22.

skeleton (A), therefore N-methyl-4', 5' : 4'', 5''-tetrahydroxy-3, 8, 6, 7-tetrahydro-(1', 2' : 1, 2; 1'', 2'' : 4, 5-dibenzoindolizinium-salt)(II) was the dehydrogenation-product. Recently Diels and Thiele¹⁾ described another example of dibenzoindolizine(IV) having skeleton(G) as the addition-product of acetylene dicarboxylic ester upon phenanthridine(III).

The present communication deals with the synthesis of 4',5':4'',5''-tetramethoxy-3,8,4,7-tetrahydro-(1',2':1,2;1'',2'':5,6-dibenzoindolizine) (VIII), a new derivative having skeleton (B), which, so far as we are aware, forms the third example of dibenzoindolizine-type of compounds.

In a previous paper from this laboratory a synthesis of 6,7-dimethoxy-3-(3', 4'-dimethoxybenzyl)-3,4-dihydroisoquinoline (V)²⁾ was reported. This was converted into N-methyl-tetrahydro-derivative (VI: R=CH₃), which was then demethylated by boiling with hydroiodic acid (VI: R=H). The latter compound is, therefore, isomeric with laudanoline, carrying dihydroxybenzyl-group on 3-position instead on 1. If the dehydrogenation-method by Robinson and Sugawara would be available upon this compound, 4', 5': 4'', 5''-tetrahydroxy-3, 8, 4, 7-tetrahydro-(1', 2': 1, 2; 1'', 2'': 5, 6-dibenzoindolizinium-salt) (VII: R=H) should be the product, which was really the case. The dehydrogenation and working up of the product were carried out exactly according to Robinson and Sugawara as shown by the following chart:—

The methods of preparation and properties of new compounds prepared during the course of the present investigation will be described briefly.

N-Methyl-6, 7-dimethoxy-3-(3', 4'-dimethoxybenzyl)-1, 2, 3, 4-tetrahydroisoquinoline (VI: R=CH₃). The methosulfate of 6, 7-dimethoxy-3-(3', 4'-dimethoxybenzyl)-3, 4-dihydroisoquinoline (V)³⁾ was reduced catalytically in alcoholic solution. The product (VI: R=CH₃) forms colour-

- 1) Journ. prakt. Chem. **156** (1940), 195.
- 2) Sugawara, Kakemi, Kazumi: Proc. **15** (1939), 223; Ber. **73** (1940), 782.
- 3) Sugawara, Kakemi, Kazumi: loc. cit.

less needless of m. p. 99° from ether. ($C_{21}H_{27}O_4N$ requires C 70.6, H 7.6, N 3.9; Found C 70.95, H 7.5, N 4.25).

The demethylation of this base was carried out by boiling it with an excess of hydroiodic acid and evaporating the latter in vac., leaving red viscous oil, which on being treated with sulphurous acid turned into colourless amorphous substance of m. p. $89-91^{\circ}$, and was identified as its tetraacetyl-derivative. The latter separates in colourless grains from benzene-petrolether and melts at $133-135^{\circ}$. ($C_{25}H_{27}O_8N$ requires C 64.0, H 5.75, N 3.0; Found C 64.3, H 5.5, N 3.4).

N-Methyl-4',5':4'',5''-tetrahydroxy-3,8,4,7-tetrahydro-(1',2':1,2;1'',2'':5,6-dibenzoindolizinium salt) (VII: R=H). The foregoing hydroiodide of tetrahydroxy-compound (VI: R=H) was converted into the acetate in alcoholic solution and dehydrogenated by means of chloranil according to Robinson and Sugasawa. Since the product was unstable in the air it was converted into O-methyl- and O-acetyl-derivatives.

N-Methyl-4',5':4'',5''-tetramethoxy-3,8,4,7-tetrahydro-(1',2':1,2;1'',2'':5,6-dibenzoindolizinium salt) (VII: R=CH₃). The aforesaid tetrahydroxy compound (VII: R=H) was methylated by means of dimethyl-sulfate and aqueous alkali in the atomosphere of nitrogen, and the methylated iodide (VII: R=CH₃, X=I) was isolated as usual. It forms colourless sandy crystals from pure methanol and melts at $248-249^{\circ}$ under decomposition. ($C_{21}H_{26}O_4NI$ requires C 52.1, H 5.4, N 2.9: Found C 51.8, H 5.1, N 3.2).

4',5':4'',5''-Tetramethoxy-3,8,4,7-tetrahydro-(1',2':1,2;1'',2'':5,6-dibenzoindolizine) (VIII). The foregoing iodide was converted into the corresponding chloride and the latter was heated in vac. at $215-220^{\circ}$ until the effervescence had ceased. The residue, light coloured viscous substance, was purified from pure alcohol, forming faintly coloured plates melting and blackening at $146-147^{\circ}$. In conformity with its constitution as a dihydroindole-derivative, it is easily oxidisable in the air and soon turns yellow on scrubbing on a porous plate. The faint but distinct Ehrlich's colour-test shows that this compound is contaminated with indole-derivative, though it analyzes correctly as the indoline. $C_{20}H_{23}O_4N$ requires C 70.4, H 6.7, N 4.1; Found C 70.4, H 6.7, N 4.3).

Tetra-acetyl-derivative (X). When N-methyl-tetrahydroxy-indolizinium-chloride (VII: R=H) was acetylated by means of acetic anhydride in the presence of pyridine the tetra-acetylindolizine was produced, CH₃·X-group being removed during the acetylation-process, probably due to the feeble basicity of the resulting tetra-acetoxyindolizinium-salt; the similar fact was also observed in the former case¹⁾. Purified from alcohol it forms slightly coloured scales of m. p. $198-200^{\circ}$. From the fact that it gives distinct Ehrlich's colour-test and from the results of analyses formula (X), 4',5':4'',5''-tetraacetoxy-4,7-dihydro-(1',2':1,2;1'',2'':5,6-dibenzoindolizine), was assigned to this substance. ($C_{24}H_{21}O_8N$ requires C 63.9, H 4.7, N 3.1: Found C 64.25, 64.3; H 5.0, 4.85; N 3.4).

The dehydrogenation of tetramethoxy-tetrahydro-dibenzoindolizine

1) Robinson, Sugasawa: loc. cit.

carried out by bubbling air through the boiling alcoholic solution in the presence of platinum-black. The product forms faint yellow needles of m. p. 193-194° giving deep purple-red Ehrlich-test, for which we propose provisionally formula (IX) from the result of analysis. ($C_{20}H_{19}O_4N$ requires C 71.2, H 5.6; Found C 71.3, H 5.85).

The work in dibenzoindolizine-series will be continued.

We are indebted to the Imperial Academy of Japan for research grants.

All analyses were executed by Miss Serikawa and Miss Takahashi.