Notes

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Yoshio Ban and Masako Seo: The Synthesis of β-Carboline Derivatives. III.[*1] A Synthesis of 10-Methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium Salts.

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In the course of studies on the total synthesis of alstoniline (I),1) an attempt was made with success to improve the yield of the entitled compounds (IVa and b) prepared by our synthetic method for β-carboline derivatives,1,2) as is indicated in the following scheme.

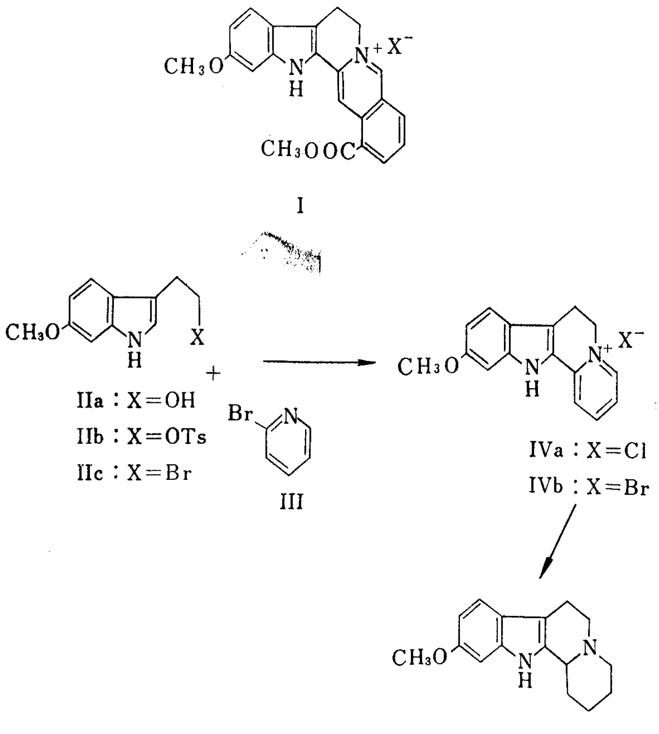

Chart 1.

6-Methoxytryptophol (IIa)3) was condensed with tosyl chloride in pyridine at −10° to afford the corresponding tosylate (IIb) in 78% yield as the pale yellow amorphous powder, m.p. 81~82°, which is rather unstable and becomes a greenish resin on exposure to air.

Thus, the tosylate (IIb) was immediately used for the condensation with 2-bromopyridine (III). A solution of IIb in the large excess of III was heated to 60~70° under a stream of nitrogen for 10 hours to afford 10-methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium chloride (IVa), m.p. 288° (decomp.) in 89.3% yield after one recrystallization

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[*1] Part II. Y. Ban, M. Seo: Tetrahedron, **16**, 11 (1961).

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1) Y. Ban, M. Seo: J. Org. Chem., **27**, 3380 (1962).

2) *Idem*: Chem. & Ind. (London), 235 (1960); Tetrahedron, **16**, 5 (1961).

3) R.C. Elderfield, B.A. Fischer: J. Org. Chem., **23**, 949 (1958).

from methanol, which is the best record so far described for this type of condensations.[1,2] In the case of substituting IIc for IIb in the similar synthesis, the yield resulted in only about 35% as the bromide (IVb), yellow orange needles, m.p. 304° (decomp.), after one recrystallization from ethanol. The physicochemical properties of IVb are in good agreement with the description (yellow orange needles, m.p. 306~307° (decomp.)) and the ultraviolet absorption spectrum for the same compound synthesized by Elderfield[4] *via* the other route.

The bromide (IIc) is prepared from 6-methoxytryptophol (IIa) in a rather poor yield and the present condensation with the tosylate (IIb) is much better than with the bromide (IIc). Therefore, the method of using the tosylate (IIb) as a component of this condensation seems to be generally advantageous for the synthesis of this type of quinolizinium salts.

The quaternary chloride (IVa) was hydrogenated with Adams' catalyst to afford the 10-methoxy-1, 2, 3, 4, 6, 7, 12, 12*b*-octahydroindolo[2, 3-*a*]quinolizine (V), small colorless needles, m.p. 201~202°. The pharmacological effects of these compounds are being tested.

Experimental[*3]

6-Methoxytryptophol Tosylate (IIb)——In 2.5 ml. of anhyd. pyridine cooled to −10° was dissolved freshly prepared tosylchloride (420 mg., 1.1 mol. equiv.), to which 6-methoxytryptophol (IIa, 382 mg. 1.0 mol. equiv.) was added and the resulting mixture was again cooled to −10°. After about 1 hr. kept at the above temperature, pyridine hydrochloride began to deposit, and the mixture was allowed to stand for an additional 2 hr., to which 5*N* H_2SO_4 (6 ml.) was added all at once. An oily product that separated was rubbed to solidify and the solid was collected on a filter, washed with H_2O until the washing indicated not to be acidic, and then washed with hexane till the solid became negative at the Beilstein test. After drying, there was obtained 540 mg. (yield 78%) of a pale yellow powder, m.p. 81~82°, which became a greenish resin either on exposure to air or when kept as an Et_2O or benzene solution.

10-Methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium salts (IV)——a) 6-methoxytryptophol tosylate (IIb, 210 mg.) was dissolved in 2-bromopyridine (III, 1.45 g.) and the resulting soluting was heated to 60~70° under a stream of N_2 for 10 hr. In 10 min. after the start of heating, the color of the solution changed from yellow-green to red, and in 20 or 30 min, yellow needles began to deposit. On cooling, the reaction mixture was triturated with absolute Et_2O to remove 2-bromopyridine salt and the other starting materials, and 230 mg. (93.8%) of the brownish yellow powder was collected. This product was treated with AgCl in the usual manner, and the resulting product was recrystallized from MeOH to afford 155.8 mg.(89.3%) of orange yellow needles, m.p. 288°(decomp.), containing no sulfur. This was identified with the material prepared according to the (b) method by mixed melting point test, and IR and UV spectral comparisons. *Anal.* Calcd. for $C_{16}H_{15}N_2OCl\cdot\frac{1}{2}H_2O$: C, 64.98; H, 5.41; N, 9.47. Found: C, 65.31; H, 5.05 ; N, 9.72.

b) A solution of 3-(2-bromoethyl)-6-methoxyindole (172 mg.) and 2-bromopyridine (214 mg.) in anhyd. benzene (7 ml.) was refluxed under a stream of N_2 for 11 hr. On cooling there was added dry Et_2O to dissolve the starting materials, and 142.5 mg. (63.4%) of a brownish yellow powder was collected on a filter. Recrystallization from EtOH gave 79 mg. (35%) of yellow orange needles, m.p. 304° (decomp.), whose UV absorption and melting point were in good agreement with the descriptions by Elderfield.[4] UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε) : 424 (4.18), 335 (4.07), 266 (3.72); $\lambda_{\min}^{\text{EtOH}}$ mμ (log ε) : 369 (3.79), 290 (3.29), 250 (3.45).

The bromide was treated with AgCl in MeOH to yield the corresponding chloride, orange yellow needles, m.p. 288° (decomp.) which is identical with the chloride prepared by the a) method.

10-Methoxy-1,2,3,4,6,7,12,12*b*-octahydroindolo[2,3-*a*]quinolizine (V)——A solution of the foregoing quaternary chloride (IVa, 200 mg.) in 50% MeOH (40 ml.) was subjected to hydrogenation over Adams' catalyst at room temperature under atmospheric pressure of H_2. In 4 or 5 hr., the yellow color of the solution completely disappeared, and its UV absorption became in good agreement with that of 6-methoxyindole, indicating the absence of the starting material. After filtration of the catalyst and evaporation of the solvent *in vacuo*, there remained 160 mg. of the hydrochloride, m.p. 266~268°, which was dissolved in hydr. MeOH and the resulting solution was basified with 10% Na_2CO_3 solution. The precipitate collected on a filter, was recrystallized from a mixture of hexane and Et_2O to afford 130

[*3] All melting points are uncorrected.

4) R.C. Eldefield, J.M. Lagowski, O.L. McCurdy, S.L. Wythe : J. Org. Chem., **23**, 435 (1958).

mg. (73%) of small colorless needles, m.p. 201～202°. *Anal.* Calcd. for $C_{16}H_{20}N_2O$: C, 75.00; H, 7.81; N, 10.93. Found: C, 74.98; N, 7.85; N, 10.77.

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Summary

10-Methoxy-6,7-dihydro-12*H*-indolo[2,3-*a*]quinolizinium salts were prepared in ca. 90% yield through condensation of 6-methoxytryptophol tosylate with 2-bromopyridine, which is the best record so far described for this type of condensations. The above salt was hydrogenated to the octahydroindolo[2,3-*a*]quinolizine derivative.

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Takeshi Oishi, Shizuo Maeno, and Yoshio Ban: The Synthesis of 3-Spirooxindole Derivatives. IV.[*1] The Conversion of 3-Spirooxindole to Indole Derivative.

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In the previous paper of this series,[1] there was reported a synthesis of the 3-spirooxindole (I), which was identified with the Julian's compound, m.p. 182°.[2] This identification conclusively established Belleau's formula (I)[3] for the above substance, to which Julian had given the formula (II).[2] Meanwhile, Julian reduced this compound with the limited amount of lithium aluminum hydride and then treated it with hydrochloric acid to obtain the indole derivative (III).[2b] Based upon the correct formula (I) for the starting material, this conversion is interpreted to progress as is indicated in the Chart (I→III), which may be accepted as a typical Wagner-Meerwein rearrangement.

These works prompted us to try the conversion of 3-spirooxindole (IV) to the indole derivative (VI) *via* the intermediate (V), as a preliminary for the chemical correlation of N-methylrhynchophyllane (X) with N-methyldihydrocorynantheane (XI).

Thus, the 3-spirooxindole (IV) which was prepared by us,[4] was subjected to the reduction with 3/4 molar equivalent of lithium aluminum hydride, followed by treatment of hydrochloric acid to afford a mixture of the crude bases, which were separated by chromatography. Elution with benzene gave colorless prisms, m.p. 58～60°, which were identified with the indoline (IX).[4] The combined fractions eluted with benzene-

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[*1] Part III, This Bulletin, **11**, 451 (1963).

[*2] Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (大石　武，前野倭男，伴　義雄).

[1] Y. Ban, T. Oishi: Chem. & Ind. (London), 349 (1960); This Bulletin, **11**, 441 (1963).

[2] *a*) P.L. Julian, A. Magnani, J. Pikl, W.J. Karpel: J. Am. Chem. Soc., **70**, 174 (1948). *b*) P.L. Julian, A. Magnani: *Ibid.*, **71**, 3207 (1949).

[3] B. Belleau: Chem. & Ind. (London), 229 (1955).

[4] Y. Ban, T. Oishi: This Bulletin, **11**, 446 (1963).