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165. Sadao Ohki*1 and Ichiro Matuo*2: Synthesis of Quinolizine Derivatives. IX.[1] Synthesis of 3,3′-Polymethylenediquinolizidine.

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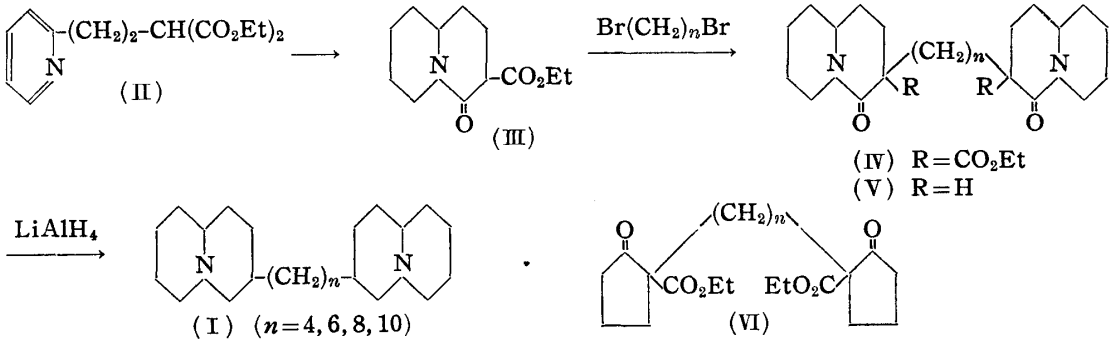
Polymethylene-diammonium-type compounds, in general, possess a strong curariform activity and are considered to constitute the main active component of *d*-tubocurarine chloride. For example, decamethonium bromide (or iodide) is used for medical treatment.

On the other hand, curariform activity is observed in chemical compounds which have quinolizidine or indolizidine ring in their structure. For instance, canadine and erythrina alkaloid possess either quinolizidine or indolizidine ring. Boekelheide and others synthesized many quinolizidine derivatives and tested their biological activity, but they could not find any derivatives among such synthesized compounds which show marked curariform activity.[2]

Attempts were made to introduce a quinolizidine ring into compounds of polymethylene-diammonium-type to obtain various derivatives (I: dimethiodide) systematically and their biological action was tested using experimental animals such as frogs and rabbits. The purpose of the present work is to obtain some curariform-active compounds with less undesirable side-effects on respiratory function and others, which are commonly seen among usual curare substances.

3-Ethoxycarbonyl-4-oxoquinolizidine (III) was synthesized by the reductive cyclization of diethyl 2-(2-pyridyl)ethylmalonate (II), using platinum oxide or Raney nickel catalyst as usual.[2,3] In addition, rhodium catalyst (5% rhodium on activated alumina) was also used at room temperature and atmospheric pressure for the same purpose. To obtain 3,3′-polymethylene-3,3′-diethoxycarbonyl-4,4′-dioxo-diquinolizidine (IV), condensation of potassium salt of (III) with polymethylene bromide was carried out in dehyd. xylene. The final product of the above process dose not decolorize potassium permanganate or bromine and therefore alkyl derivatives of (III) may not be O-alkyl but C-alkyl derivatives. The crude (IV) was hydrolyzed with potassium hydroxide in 50% ethanol and decarboxylated by heating to afford 3,3′-polymethylene-4,4′-dioxo-diquinolizidine (V). The latter was then reduced with lithium aluminum hydride in tetrahydrofuran to form 3,3′-polymethylenediquinolizidine (I). Yield of (I) from (III) was approximately 30~40%. Attempt to obtain 3,3′-ethylene-diquinolizidine in the same way failed, for unknown



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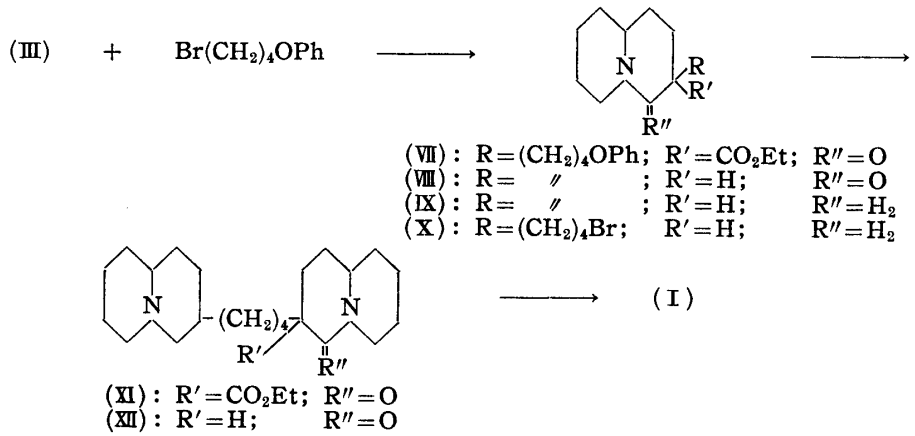
1) Part VIII: Yakugaku Zasshi, **79**, 1522(1959).
2) V. Boekelheide, *et al.*: J. Am. Chem. Soc., **71**., 879(1949).
3) S. Ohki, Y. Noike: Yakugaku Zasshi, **72**, 490(1952).

reasons but it may be due to stereochemical interference. Mayer[4] reported that in condensation of potassium salt of 2-ethoxycarbonylcyclopentanone with polymethylene bromide it was impossible to obtain mono- and di-methylenedicyclopentanone derivatives in spite of the formation of tetra- and hexa-methylene compounds (VI). The explanation of this fact seems apparently difficult but he suggested a stereochemical interference.

In (I) there may exist four racemates and two *meso*-forms provided the quinolizidine ring in (I) takes merely the most stable conformation of *trans*-chair-chair form.*3 Attempt was made to isolate these three isomers from the synthesis of (I : $n=4$) and three kinds of picrate melting at 216°, 235°, and 225~227°*4 were obtained, but their stereochemical structure was not determined.

Methiodides of (I : $n=4$, 6, 8, and 10) were prepared and their melting points were as follows : $n=4$, 291~292°; $n=6$, 305~306°; $n=8$, 224°; $n=10$, 258~260° (all melting with decomposition after 5~10° of sintering). These derivatives are considered to be a mixture of stereoisomers.

As mentioned previously, the yield of (I) varies from 30% to 40% in the method described above. To get a better yield the above method was more or less modified and the following procedure was attempted for synthesis of (I : $n=4$). In the course of the reaction from (III) to (IV), 1-bromo-4-phenoxybutane was used instead of tetramethylene bromide and the condensation product was hydrolyzed and decarboxylated, followed by reduction with lithium aluminum hydride to obtain 3-(4-phenoxybutyl)quinolizidine (IX). 3-(4-Bromobutyl)quinolizidine (X) was prepared by heating (IX) in a sealed tube containing acetic acid saturated with hydrogen bromide and condensed with (III) to obtain 3,3'-tetramethylene-3-ethoxycarbonyl-4-oxodiquinolizidine (XI). The yield of (XI) was very low and considerable amount of resinous precipitate was observed in xylene. This precipitate would consist of a quaternary base and resin resulting from intramolecular cyclization or condensation of two molecules, prior to condensation between (X) and (III). (XI) was then hydrolyzed and decarboxylated, followed by reduction with lithium aluminum hydride to form (I : $n=4$). Thus, (I : $n=4$) was obtained through two synthetic methods as described above and methiodides of (I : $n=4$) obtained by these two processes melted with decomposition at 291~292° (after sintering), either alone or in admixture. In addition, both gave almost the same infrared spectral results.



*3 Infrared absorption spectrum of (I : $n=6$) exhibited a strong absorption in the region of 2800~2700 cm^{-1} which was pointed out by Bohlmann as the absorption of *trans*-quinolizidine compound (cf. Chem. Ber., **91**, 2157(1958)).

*4 It is still not clear whether the picrate of m.p. 225~227° is a unity or a mixture of those of m.p. 216° and of 235°.

4) R. Mayer, E. Alder : Chem. Ber., 88, 1866(1955).

Curariform activity of (I) was examined in comparison with tubocurarine chloride. The compounds of (I) with $n=4$ and $n=6$ showed about one-fourth the activity of tubocurarine, while toxity of these was 6 and 10 times greater than that of tubocurarine chloride. The same test is now in progress with the products which have 8 and 10 methylene groups. The product with $n=10$ showed a significant antibacterial and antifungal activity, the results of which will be described and discussed in detail later.

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Experimental

3-Ethoxycarbonyl-4-oxoquinolizidine (III)—A mixture of diethyl 2-(2-pyridyl)ethylmalonate (II) (66 g.), MeOH (100 cc.), AcOH (20 g.), and 1.5 g. of Rh-Al_2O_3 was reduced with H_2 at ordinary temperature and pressure. The uptake of H_2 was completed in 30 hr. After removal of the catalyst, the solvent was distilled off and the residue was dissolved in water. The solution was basified with Na_2CO_3, extracted with Et_2O, and Et_2O was removed after drying over Na_2SO_4. The residue was heated at 200~210° for 20 min. and distilled *in vacuo*. Pale yellow oil, $b.p_2$ 165°; yield, 47 g.

3,3′-Tetramethylene-3,3′-dioxodiquinolizidine (V : $n=4$)—To a suspension of 3.6 g. of K powder in 150 cc. of dehyd. xylene a solution of 20 g. of (III) in 50 cc. of dehyd. xylene was added slowly with stirring. After heating at 130° for 3 hr. with stirring a clear solution of K salt of (III) was obtained. To this solution, a solution of 9.0 g. of tetramethylene bromide in 50 cc. of dehyd. xylene was added dropwise and the mixture was heated at 135~140° with stirring for 15 hr. After cooling and separation of KBr by filtration, the solution was washed with a small quantity of water and dried over Na_2SO_4. Xylene was removed *in vacuo* and the residue was obtained as viscous oil; yield, 22 g.

A mixture of 22 g. of the crude oil described above and ethanolic KOH (5 g. in 80 cc. of hydr. EtOH) was boiled for about 6 hr. on a water bath. After removal of EtOH by distillation, the residue was dissolved in 40 cc. of water and shaken with Et_2O to remove the unreacted substances. The aqueous layer was acidified with AcOH and extracted several times with a faintly warm benzene (total 200 cc.), the benzene layer was washed with a small quantity of saturated NaCl solution, and dried over Na_2SO_4. After benzene was removed *in vacuo*, the residual oil was heated at 160° for 1 hr. under a reduced pressure. After cool the syrupy residue was extracted with 200 cc. of Et_2O, the Et_2O layer was washed with 30 cc. of 10% NaOH, and dried over Na_2SO_4. The removal of Et_2O gave viscous oil which was purified by chromathography on alumina with benzene and 11.4 g. of pale yellow, viscous oil (V : $n=4$) was obtained. Attempted distillation or crystallization of its derivatives was unsuccessful.

3,3′-Tetramethylene-diquinolizidine (I : $n=4$)—To a solution of 2.1 g. of $LiAlH_4$ dissolved in 70 cc. of dehyd. tetrahydrofuran, while chilled with ice, a solution of 11.4 g. of the crude oil (V : $n=4$) in 60 cc. of dehyd. tetrahydrofuran was dropped in slowly by which the mixture became turbid. The mixture was refluxed on a water bath for 10 hr., 10% NaOH was added slowly, while chilled in ice, to decompose the excess of $LiAlH_4$, and then salted out with K_2CO_3. After separation of the tetrahydrofuran layer, the aqueous layer was extracted with Et_2O (100 cc.). The combined solution was dried over Na_2SO_4. After removal of the solvents, the residue was distilled *in vacuo*. Pale yellow oil, $b.p_{3.0}$ 190~195°; yield, 5.5 g.

Methiodide : Colorless plates, m.p. 291~292° (decomp., after sintering at about 280°) (from EtOH). *Anal.* Calcd. for $C_{24}H_{46}N_2I_2$: C, 46.75; H, 7.45; N, 4.54. Found : C, 47.20; H, 7.04; N, 4.46.

Separation of the Stereoisomers of (I : $n=4$)—A solution of 0.5 g. of (I : $n=4$) dissolved in dehyd. Et_2O was chromatographed on alumina (2×20 cm.) and following result was obtained.

Fraction	Eluant	Vol. (cc.)	Wt. (g.)	Picrate m.p. (°C)
1	Et_2O	25	0.07	235~237
2~3	〃	50	0.38	235~237 (and 225~227)
4~5	〃	50	0.02	215~217
6	Benzene	50	trace	
7	MeOH	50	trace	

Anal. Calcd. for $C_{22}H_{40}N_2 \cdot 2C_6H_3O_7N_3$ ((I : $n=4$) picrate) : C, 51.64; H, 5.82; N, 14.17. Found (in the picrate of m.p. 215~217°) : C, 51.15; H, 6.25; N, 13.99. Found (in the picrate of m.p. 235~237°): C, 51.29; H, 6.09; N, 13.94. Found (in the picrate of m.p. 225~227°) : C, 51.30; H, 6.16; N, 13.85.

3,3′-Hexamethylene-, 3,3′-Octamethylene-, and 3,3′-Decamethylene-diquinolizidine(I : $n=6$, $n=8$,

and $n=10$)—These substances were synthesized by the method given for the preparation of (I : $n=4$).

(I : $n=6$) : Pale yellow oil, b.$p_{2.0}$ 155°. Yield, 3.5 g. (from 18.0 g. of (III)). Methiodide : Colorless plates (from hydr. MeOH), m.p. 305~306° (decomp., after sintering at about 300°). *Anal.* Calcd. for $C_{26}H_{50}N_2I_2$: C, 48.45; H, 7.76; N, 4.34. Found : C, 48.55; H, 7.29; N, 4.14.

(I : $n=8$) : Pale yellow oil, b.$p_{1.0}$ 180°. Yield, 1.0 g. (from 4.24 g. of (III)). Methiodide : Colorless plates (from MeOH and AcOEt), m.p. 224° (decomp. after sintering at about 220°). *Anal.* Calcd. for $C_{28}H_{54}N_2I_2$: C, 50.00; H, 8.03; N, 4.16. Found : C, 50.04; H, 7.75; N, 4.11.

(I : $n=10$) : Pale yellow oil, b.$p_{1.0}$ 180°. Yield, 2.6 g. (from 8.0 g. of (III)). Methiodide : Colorless plates (from EtOH and AcOEt), m.p. 258~260° (decomp. after sintering at about 255°). *Anal.* Calcd. for $C_{30}H_{58}N_2I_2$: C, 51.41; H, 8.28; N, 4.00. Found : C, 51.29; H, 8·10; N, 4.05.

3-(4-Phenoxybutyl)quinolizidine (IX)—To a solution of K salt of (III) in dehyd. xylene (prepared from 3.9 g. of K and 22 g. of (III) according to the foregoing method) a solution of 28 g. of 1-phenoxy-4-bromobutane in 100 cc. of dehyd. xylene was dropped in during 1 hr. and the mixture was heated at 135~140° with stirring for 15 hr. After cooling and separation of KBr by filtration, the solution was washed with a small quantity of water and dried over Na_2SO_4. Xylene was removed *in vacuo* and the residue was obtained as yellow viscous oil, which was purified by chromatography on alumina; yield, 28 g. This oil (28 g.) was mixed with ethanolic KOH (12 g. in 150 cc. of hydr. EtOH) and boiled for 8 hr. on a water bath. After removal of EtOH by distillation, the residue was dissolved in 40 cc. of water and shaken with Et_2O to remove the unreacted substances. The aqueous layer was acidified with AcOH, extracted with a faintly warm benzene (total 200 cc.), the benzene layer was washed with a small quantity of saturated NaCl solution, and dried over Na_2SO_4. After removal of benzene, the residual oil was heated at 160~170° for 1 hr. to effect decarboxylation. After cool, the syrupy residue was dissolved in benzene (50 cc.), the benzene layer was washed with 10% NaOH, and dried over Na_2SO_4. The removal of benzene gave viscous oil which was distilled *in vacuo* and a pale yellow oil (VIII), b.$p_{4.0}$ 230°, was obtained. Yield, 14.2 g.

A solution of 14.2 g. of (VIII) in 100 cc. of dehyd. Et_2O was added dropwise with cooling and stirring to a solution of 2.0 g. of $LiAlH_4$ in 200 cc. of dehyd. Et_2O by which the mixture became turbid. After refluxing on a water bath for 8 hr. with stirring, water was added with cooling to decompose the excess of $LiAlH_4$ and separated Et_2O layer was dried over Na_2SO_4. Et_2O was removed and the residue was distilled *in vacuo*. Pale yellow oil, b.$p_{4\sim5}$ 115~118°. Yield, 10.0 g. This oil gradually crystallized, melted at 45~70°, and gave two kinds of crystals by chromatography on alumina with petr. ether and several recrystallizations from hydr. MeOH; one of colorless plates, m.p. 60°, and the other of m.p. 79~80°. The two are stereoisomers. *Anal.* Calcd. for $C_{19}H_{29}ON$: C, 79.39; H, 10.17; N, 4.87. Found (in the substance of m.p. 60°) : C, 79.61; H, 9.92; N, 4.43. Found (in the substance of m.p. 79~80°) : C, 79.56; H, 10.19; N, 4.80.

(I : $n=4$) from (IX)—A solution of 3.0 g. of (IX) (m.p. 45~70°) in 15 cc. of AcOH was saturated with HBr while chilled with ice and heated in a sealed tube for 10 hr. in an oil bath (120~130°). After removal of AcOH under a reduced pressure, the residual oil was dissolved in water and basified with Na_2CO_3. The oily substance that separated was extracted with benzene after salting out with K_2CO_3. The benzene layer was washed with a small quantity of water, dried over Na_2SO_4, and the benzene removed *in vacuo*. There was obtained 3.0 g. of brownish oil (X).

The condensation of this crude oil (3.0 g.) with K salt of (III) (prepared from 0.6 g. of K and 4.0 g. of (III)) and subsequent decarboxylation was carried out according to the procedure given for the preparation of (V) and (VIII). In this case only 0.2 g. of the objective substance, 3,3′-tetramethylene-4-oxodiquinolizidine (XII), was obtained as a yellow oil. This oil was reduced with $LiAlH_4$ in dehyd. Et_2O according to the procedure given for the reduction of (VIII). There was obtained 0.15 g. of pale yellow oil which gave a methiodide of colorless plates, m.p. 291~292° (decomp., after sintering). A mixture of this methiodide with the foregoing methiodide of m.p. 291~292° (decomp., after sintering) showed no depression of the melting point and their infrared absorption spectra were identical.

Summary

In expectation of a curariform activity with little side effects, methiodide of 3,3′-polymethylenediquinolizidines (I : $n=4$, 6, 8, and 10) were synthesized. Condensation of the potassium salt of 3-ethoxycarbonyl-4-oxoquinolizidine and polymethylene bromide, followed by saponification and decarboxylation, and reduction with lithium aluminum hydride of the lactam compound so obtained afforded the objective compounds (I). (I: $n=4$) was also obtained through 3-(4-phenoxybutyl)quinolizidine (IX) as an intermediate and compounds obtained by the two procedures were found to be identical. The curariform activity of (I) ($n=4$ and 6) was one-quarter that of tubocurarine chloride while their toxicity was 6 and 10 times, respectively, of tubocurarine. The compound with $n=10$ had a strong antibacterial and antifungal activity.

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