79. **Toshiro Fujisawa**: Synthesis of 2,2′-Polymethylene-bis(*Py*-tetrahydroisoquinoline) Derivatives. II.[1] Synthesis of 2,2′-Polymethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline)*

(*Research Laboratories of the Institute of Pharmaceutical Resources***)

Some time ago, Sugasawa and the writer reported[1] that 2,2′-ethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) can easily be synthesized in a comparatively good yield from ethylenediamine and 6-bromomethylsafrole, derived from safrole, as part of studies on the utilization of safrole as a raw material for medicinals and that this method might be utilized for the syntheses of 2,2′-polymethylene-bis(*Py*-tetrahydroisoquinolines) in general.

Barlow and Ing[2] prepared a series of bis(trimethyl)ammonium compounds possessing a methylene group in the middle and found that the decamethylene compounds possessed the strongest curare-like action. The same facts were also confirmed independently by Paton and Zeimis.[3] On the other hand, Kimura and Unna[4] measured the distance between the two nitrogen atoms in *d*-tubocurarine chloride and decamethonium (C_{10}) and showed the distance to be 13~15 Å in the former and 15 Å in the latter.

Based on these facts, Taylor synthesized quaternary ammonium salts with heterocyclic compounds possessing decamethylene with nitrogen atoms at both ends[5] and later, those possessing eight to twelve methylene groups,[6] to examine their curare-like action.

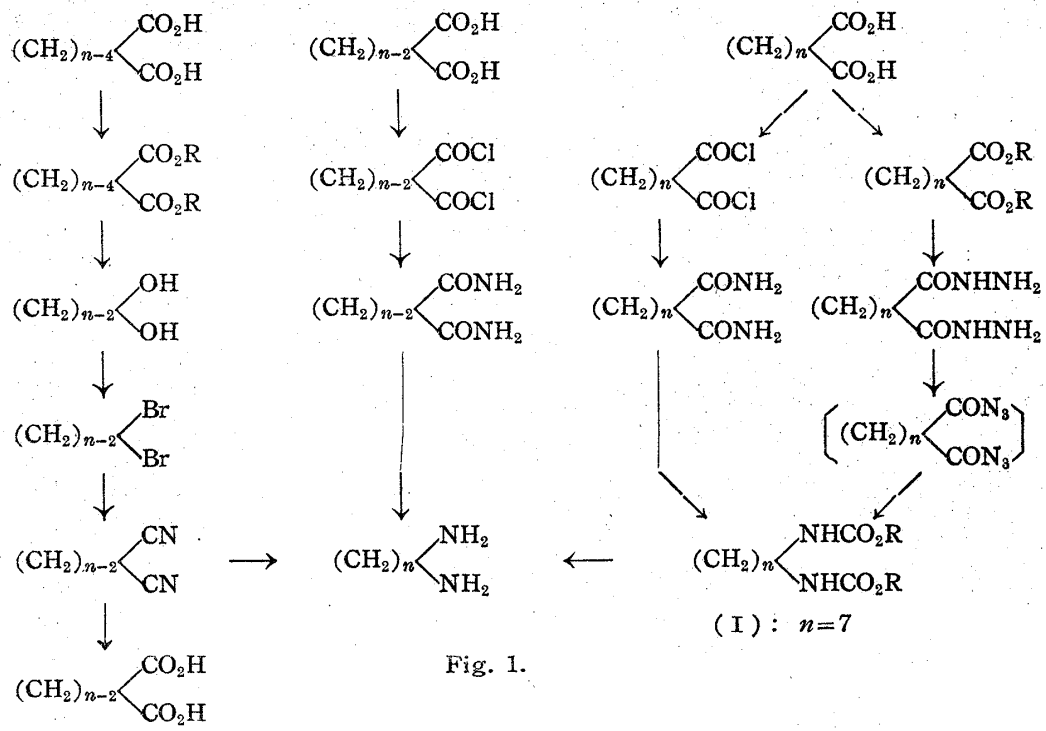


Fig. 1.

* Studies on the Utilization of Safrole as Medical Raw Material. VIII.(2).

** Nukui, Koganei-machi, Kitatama-gun, Tokyo (藤沢俊郎).

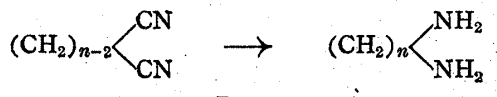
1) S. Sugasawa, T. Fujisawa: This Bulletin, **1**, 80(1953).
2) R. B. Barlow, H. R. Ing: Nature, **161**, 718(1948).
3) W. D. M. Paton, E. J. Zeimis: *Ibid.*, **161**, 718(1948).
4) K. K. Kimura, K. Unna: J. Pharmacol. Exptl. Therap., **95**, 149(1949).
5) E. P. Taylor: J. Chem. Soc., **1951**, 1150.
6) *Ibid.*, **1952**, 142, 1309.

In the present series of experiments, seven kinds of bis(*Py*-tetrahydroisoquinoline) derivatives with six to twelve methylene groups between the isoquinoline nuclei were prepared by the utilization of the condensation of 2,3-methylenedioxy-5-(*β*-bromopropyl)-6-bromomethylbenzene and polymethylenediamines and the relationship, if any, between the curare-like action and the number of methylene groups was examined, the results of which are described in this paper. Pharmacological action is being examined and will be reported at a later date.

Polymethylenediamines were obtained from various polymethylenedicarboxylic acids by the Hofmann or Curtius degradation, or by the reduction of nitriles or acid amides as shown in Fig. 1.

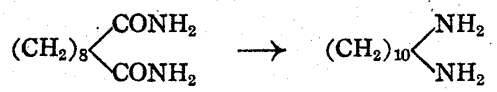
The polymethylene-dicarboxylic acids were confirmed by their melting points and those of acid anilides after recrystallization. Of the polymethylenediamines used, hexa-

Table I. Nonamethylene-, Decamethylene-, Undecamethylene-, and Dodecamethylene-diamines.



	Raw material			React. condn.		Diamine		
						b.p.	Yield	
n	Nitrile (g.)	$LiAlH_4$ (g.)	Ether (cc.)	Temp. time (hr.) ice-cool.	Reflux. time (hr.)	°C/mm. Hg	g.	%
9	3.2	1.2	120	1	1	145~148/12	2.0	67
10	3.4	1.2	120	1	1	140/12	2.4	67
11	8.0	3.0	150	0.5	0.5	138/5	6.9	56
12	12.2	3.6	230	0.25	0.25	135~138/3	8.7	68

After the decomposition of $LiAlH_4$ with a small amount of water, the residue was decomposed with Rochelle salt, and the diamines were obtained by continuous extraction.



n	Amide	$LiAlH_4$	Solvent	React. condn.		Diamine b.p. °C/mm. Hg	g.	yield %
10	5.0 g.	2.8 g.	Ether, 100 cc. Tetrahydrofuran, 100 cc.	30° 1 hr.	Reflux. 10 hrs.	153/18	1.3	42

$NH_2(CH_2)_nNH_2$

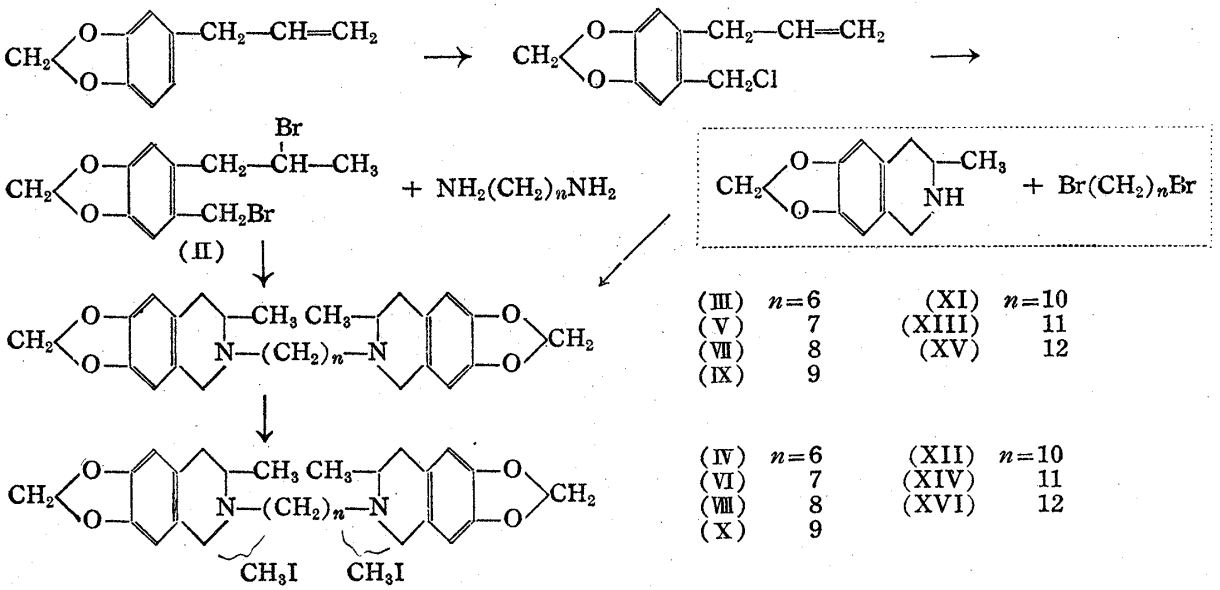
					Elemental analyses					
					Calcd., %			Found, %		
n	Preparative method	b.p. °C/mm. Hg	Dipicrate m.p., °C (* Analyzed)	Dipicrolonate m.p., °C	C	H	N	C	H	N
6	Market prod.	194~195	219(dec.)[a]*		37.63	3.83	19.51	37.68	3.77	19.51
7	Hofmann or Curtius degrn. of azelaic acid	115~117/8[b]	177(dec.)[c]*		38.77	4.08	19.04	39.22	3.76	18.73
8	Curtius degrn. of sebacic acid	104~106/8[d]	184(dec.)[e]*	245(dec.)*	39.86	4.31	18.60	40.03	4.30	18.54
9	Redn. of $(CH_2)_7(CN)_2$ with $LiAlH_4$	145~148/12[f]		245(dec.)*	50.73	5.54	20.41	50.70	5.91	20.38
10	Redn. of $(CH_2)_8(CN)_2$ or $(CH_2)_8(CONH_2)_2$ with $LiAlH_4$	153/18[g]		+H_2O 246(dec.)*	50.13	5.84	19.49	50.12	6.14	19.43
11[h]	Redn. of $(CH_2)_9(CN)_2$ with $LiAlH_4$	138~142/5~6	119~122	239(dec.)*	52.10	5.88	19.61	51.76	5.94	19.48
12[i]	Redn. of $(CH_2)_{10}(CN)_2$ with $LiAlH_4$	135~138/3	163~165	235(dec.)*	52.75	6.04	19.24	52.45	6.06	18.79

a) Ssolonina : J. Russ. Phys. Chem. Soc., **28**, 561; Bull. soc. chim. France, [3] **16**, 1880. *b*) J. Russ. Phys. Chem. Soc., **28**, 562. *c*) *Ibid.*, **28**, 563. *d*) Steller : J. prakt. Chem., [2] **62**, 223, 226. *e*) Steller : *Ibid.*, [2] **62**, 229. *f*) Ssolonina : J. Russ. Phys. Chem. Soc., **29**, 411; Chem. Zentr., **1897** II, 849. *g*) Rhookan, Krafft : Ber., **25**, 2253. *h*) v. Braun : *Ibid.*, **45**, 1975. *i*) v. Braun : *Ibid.*, **42**, 4553.

methylenediamine was a market product. Heptamethylenediamine was obtained by the Curtius degradation from azelaic ester through the hydrazide and diurethane (I) to heptamethylenediamine hydrochloride or by the Hofmann degradation from azelaic acid amide through the diurethane (I). Octamethylenediamine was obtained by the Curtius degradation[7], and nona- to dodecamethylenediamines were obtained from the corresponding acids through their esters, glycols (by lithium aluminum hydride), dibromides, and anilides, with final reduction with lithium aluminum hydride. Decamethylenediamine was also obtained by the reduction of sebacic acid amide with lithium aluminum hydride.

Reaction conditions and the results in obtaining these compounds are listed in Table I.

The objective compounds were obtained by the condensation of 2,3-methylenedioxy-5-(β-bromopropyl)-6-bromomethylbenzene (II) and one of the polymethylenediamines by the same method as described in the previous paper.[1]



The structure of the compounds hereby obtained were ascertained through their elemental analyses as well as direct comparison of the few optional compounds with the products obtained by the condensation of 3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline and suitable polymethylene bromides.

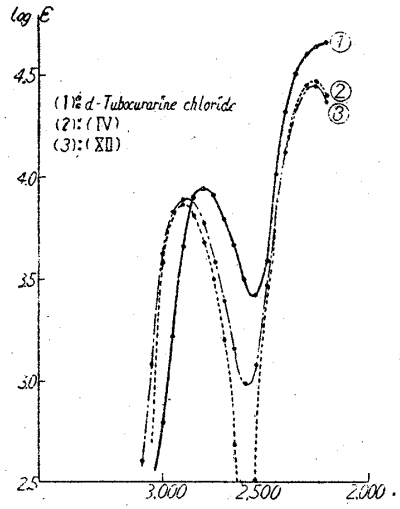


Fig. 2.

Ultraviolet Absorption Curves of *d*-Tubocurarine Chloride, and Methiodides of Hexamethylene and Decamethylene Compounds (2 mg./100 cc. solution) Beckman Spectrophotometer

7) Steller: J. prakt. Chem., [2] **62**, 233, 226.

On comparing these two methods of condensation, the method adopted in the present series of experiments is more favorable in that it requires shorter period in the condensation than that mentioned later.

The ultraviolet absorption curves of these compounds are shown in Figs. 2 and 3.

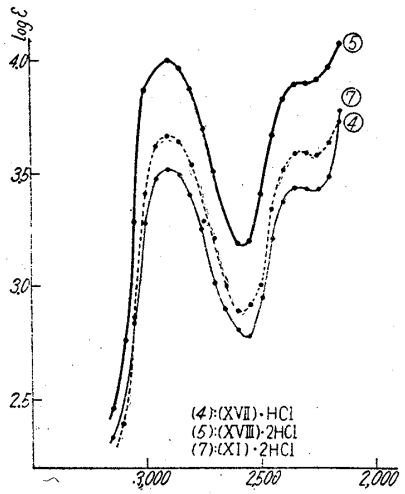


Fig. 3.

Ultraviolet Absorption Curves of 3-Methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline Hydrochloride, and Hydrochlorides of Dimethylene and Decamethylene Compounds (2 mg./100 cc.) Beckman Spectrophotometer

The writer takes this opportunity to express his deep gratitude to Prof. Sugasawa for his unfailing and kind guidance throughout the course of this work, and to Mr. Mori, the Director of this Institute, for his encouragement of this study. The writer is also indebted to Messrs. Kozo Okada and Yoshio Deguchi for their cooperation in these experiments, to Mr. Kiyoshi Mizutani for the measurement of ultraviolet absorption spectra, and to the members of the Analysis Room of the Pharmaceutical Institute, University of Tokyo, and of the Institute for Infectious Diseases, for elemental analyses. Pharmacological tests are being carried out by Mr. Saburo Tamura of the Fujisawa Pharmaceutical Industries, Ltd., results of which will be reported at a later date.

Experimental

Heptamethylenediurethane (I)—i) Curtius Degradation: Obtained by the Curtius degradation of 10 g. of azelaic dihydrazide. Yield, 11.0 g. (95%). Recrystallized from a mixture of benzene and petroleum ether as crystals of m.p. 99°.

ii) Hofmann Degradation: Obtained by the Hofmann degradation of azelaic acid amide. Yield, 5.0 g. (61%). Recrystallized from petroleum ether as crystals of m.p. 99°, undepressed on admixture with the product from (i). *Anal.* Calcd. for $C_{11}H_{22}O_4N_2$: C, 53.66; H, 8.94; N, 11.38. Found: C, 53.50; H, 8.96; N, 11.46.

2,2'-Hexamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (III)—i) A solution of 3.5 g. (2 molar ratio to diamine) of 2,3-methylenedioxy-5-(β-bromopropyl)-6-bromomethylbezene (II) dissolved in 20 cc. of pure benzene was added dropwise into a solution of 2 g. (3 molar ratio to (II)) of hexamethylenediamine dissolved in pure benzene by which some fine crystals precipitated out with a slight generation of heat. After taking 15 minutes to make the dropwise addition, the mixture was boiled on a water bath for about 5 hrs. and allowed to cool over night. The crystals that separated out were collected by filtration to 2.8 g. of hexamethylenediamine hydrobromide (rate of recovery, 97%). The filtrate and benzene washings were combined and extracted with 5 lots of 100 cc. each of 10% HCl. The acid solution was basified with aq. NH_3, the semisolid that separated out was extracted with ether, and ether was removed by distillation after drying over anhydrous Na_2SO_4. The residue gradually crystallized. Yield, 2.0 g. (80%).

Free base: Recrystallized from dehyd. EtOH to fine needle crystals, m.p. 125~128°. *Anal.* Calcd. for $C_{28}H_{36}O_4N_2$: C, 72.43; H, 7.75; N, 6.03. Found: C, 72.61; H, 7.59; N, 6.21.

Dipicrate: Recrystallized from glacial AcOH to yellow needles, m.p. 218~219°(decomp.). Dried at 65~70° at 7 mm. Hg. *Anal.* Calcd. for $C_{28}H_{36}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 52.06; H, 4.55; N, 12.14. Found: C, 52.18; H, 4.93; N, 11.97.

Some base was found to have been adsorbed on Na_2SO_4 when the ether extract was dried with this salt. This base was found to be sparingly soluble in dehyd. ether but easily soluble in benzene but remained in an oily state. The dipicrate of this base was obtained as an oil but crystallized after being left to stand for three days. Recrystallization from 10% AcOH gave yellow microcrystals, m.p. 168~172°(decomp.). Its analytical values suggest the base to be 2-aminohexamethylene-3-methyl-6,7-

methylenedioxy-*Py*-tetrahydroisoquinoline.[8] *Anal.* Calcd. for $C_{17}H_{26}O_2N_2 \cdot 2C_6H_3O_7N_3$ (Dipicrate) : C, 46.5; H, 4.02; N, 14.9. Found : C, 47.0; H, 4.0; N, 14.5.

ii) A solution of 3.3 g. of hexamethylene bromide and 10.4 g. of 3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline dissolved in 50 cc. of dehyd. benzene was refluxed for about 120 hrs. The hydrobromide of the isoquinoline that separated out was removed by filtration and the base was extracted by the usual method. Yield, 4.7 g. (75%). The crude base thereby obtained contained some of the isoquinoline compound and was therefore purified by recrystallization from EtOH to white crystals, m.p. 125~127°, undepressed by admixture with the product obtained from (i).

2,2'-Hexamethylene-bis(2,3-dimethyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinolium diiodide) (IV)—A mixture of the free amine and about 5 molar equivalents of methyl iodide in abs. MeOH was heated in a sealed tube in a boiling water bath for 2 hrs. After cool, the content was taken out, MeOH was distilled off under a reduced pressure, and the residue gradually crystallized. Yield, almost quantitative. Recystallization from a mixture of hydrated acetone and MeOH gave white microcrystals, m.p. 115~120°(decomp.). Dried at 45~50° under 2 mm. Hg. *Anal.* Calcd. for $C_{28}H_{36}O_4N_2 \cdot 2CH_3I \cdot 3H_2O$: C, 45.00; H, 6.00; N, 3.49. Found : C, 45.20; H, 6.17; N, 3.36.

2,2'-Heptamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (V)—The oily base was obtained as for the foregoing hexamethylene compound. Dipicrate : Recrystallized from EtOH to yellow microcrystals, m.p. 189~191°(decomp.). *Anal.* Calcd. for $C_{29}H_{38}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 52.56; H, 4.70; N, 11.97. Found : C, 52.57; H, 4.79; N, 12.17.

Methopicrate : The dimethiodide of (V) remained oily that (V) was derived to its methopicrate which recrystallized from 20% AcOH as yellow microcrystals, m.p. 130~140°. *Anal.* Calcd. for $C_{43}H_{48}O_{18}N_2 \cdot H_2O$: C, 52.54; H, 5.09; N, 11.4. Found : C, 52.44; H, 4.81; N, 11.35.

2,2'-Octamethylene-bis(3-methyl-6,7-methlenedioxy-*Py*-tetrahydroisoquinoline) (VII)—The oily base was derived to its dipicrate which recrystallized from 70% EtOH containing a few drops of glacial AcOH to yellow microcrystals, m.p. 195°(decomp.). *Anal.* Calcd. for $C_{30}H_{40}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 53.05; H, 4.84; N, 11.79. Found : C, 52.71; H, 4.83; N, 12.23.

Dipicrolonate : Recrystallized from EtOH to yellow microcrystals, m.p. 195~197°. *Anal.* Calcd. for $C_{30}H_{40}O_4N_2 \cdot 2C_{10}H_8O_5N_4$: C, 58.82; H, 5.49. Found : C, 59.02; H, 5.70.

Dimethiodide (VII) : The base (VII) and methyl iodide were mixed in MeOH and the crystals that precipitaed out were recrystallized from dil. EtOH to white microcrystals, m.p. 270~271°(decomp.). *Anal.* Calcd. for $C_{30}H_{40}O_4N_2 \cdot 2CH_3I \cdot H_2O$ (after drying at 60~65° under 4 mm. Hg) : C, 48.36; H, 6.05; N, 3.52. Found : C, 48.46; H, 5.99; N, 3.24. Calcd. for $C_{30}H_{40}O_4N_2 \cdot 2CH_3I$ (further dried at 100° under 3 mm.) : C, 49.48; H, 5.92. Found : C, 49.40; H, 6.16.

2,2'-Nonamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (IX)—Dipicrolonate : Recrystallized from MeOH as yellow microcrystals, m.p. 193~196°(decomp.). *Anal.* Calcd. for $C_{31}H_{42}O_4N_2 \cdot 2C_{10}H_8O_5N_4$ (dried at 70° under 2 mm. Hg) : C, 59.12; H, 5.61; N, 13.56. Found : C, 59.46; H, 5.86; N, 13.10.

Dimethiodide (X) : Recrystallized from a mixture of MeOH and EtOH to white microcrystals, m.p. 244~245°(decomp.). *Anal.* Calcd. for $C_{31}H_{42}O_4N_2 \cdot 2CH_3I \cdot H_2O$ (dried at 50~55° under 3 mm. Hg): C, 49.00; H, 6.18; N, 3.46. Found : C, 48.82; H, 6.19; N, 3.50. Calcd. for $C_{31}H_{42}O_4N_2 \cdot 2CH_3I \cdot {}^1/_2 H_2O$ (further dried at 100° under 2 mm.) : C, 49.5; H, 6.14. Found : C, 49.55; H, 6.11.

2,2'-Decamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (XI)—Hydrochloride : Recrystallized from EtOH as plates, m.p. 220~225°(decomp.). *Anal.* Calcd. for $C_{32}H_{44}O_4N_2 \cdot 2HCl \cdot H_2O$ (dried at 56~65° under 6 mm. Hg) : C, 62.84; H, 7.85; N, 4.58. Found : C, 63.08; H, 7.90; N, 5.04.

Dimethiodide (XII) : Recrystallized from a mixture of MeOH and EtOH to white scales, m.p. 231~233°(decomp.). *Anal.* Calcd. for $C_{32}H_{44}O_4N_2 \cdot 2CH_3I$: C, 50.74; H, 6.24; N, 3.48. Found : C, 50.38; H, 6.39; N, 3.54.

2,2'-Undecamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (XIII)—Dipicrolonate : Recrystallized from MeOH as yellow microcrystals, m.p. 155~175°. Dried at 55~60° under 2 mm. Hg. *Anal.* Calcd. for $C_{33}H_{46}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 2H_2O$: C, 57.92; H, 6.01; N, 12.75. Found: C, 58.26; H, 5.75; N, 12.80.

Methopicrate : Since the dimethiodide of (XIII) failed to crystallize, the base was derived to its methopicrate and recrystallized from 20% AcOH to crystals of m.p. 135~145°. Dried at 60~65° under 2 mm. Hg for 24 hrs. *Anal.* Calcd. for $C_{35}H_{52}O_4N_2 \cdot 2C_6H_2O_7N_3 \cdot H_2O$: C, 54.33; H, 5.58; N, 10.60. Found : C, 54.46; H, 5.83; N, 10.96.

2,2'-Dodecamethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (XV)—The free base recrystallized from hydrated MeOH to white microcrystals, m.p. 87~89°. *Anal.* Calcd. for $C_{34}H_{48}O_4N_2 \cdot H_2O$: C, 72.08; H, 8.83; N, 4.96. Found : C, 72.45; H, 8.63; N, 5.23.

8) cf. Libman : J. Chem. Soc., **1952**, 2305.

Dipicrolonate : Recrystallized from MeOH, m.p. 180~188° (decomp.). *Anal.* Calcd. for $C_{34}H_{48}O_4N_2 \cdot 2C_{10}H_8O_5N_4$: C, 61.22; H, 5.95; N, 13.0. Found : C, 60.75; H, 5.98; N, 13.11.

Dimethiodide (XVI) : Recrystallized from a mixture of MeOH, EtOH, and ether, m.p. 145~175° (decomp.). *Anal.* Calcd. for $C_{34}H_{48}O_4N_2 \cdot 2CH_3I \cdot 2H_2O$: C, 49.76; H, 6.68; N, 3.22. Found : C, 49.83; H, 6.85; N, 3.27.

Summary

Seven kinds of 2,2′-polymethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinolines) were obtained by the condensation of 2,3-methylenedioxy-5-(β-bromopropyl)-6-bromomethylbenzene and polymethylenediamines. The presence of curare-like actions in these compounds were examined with their dimethiodides.

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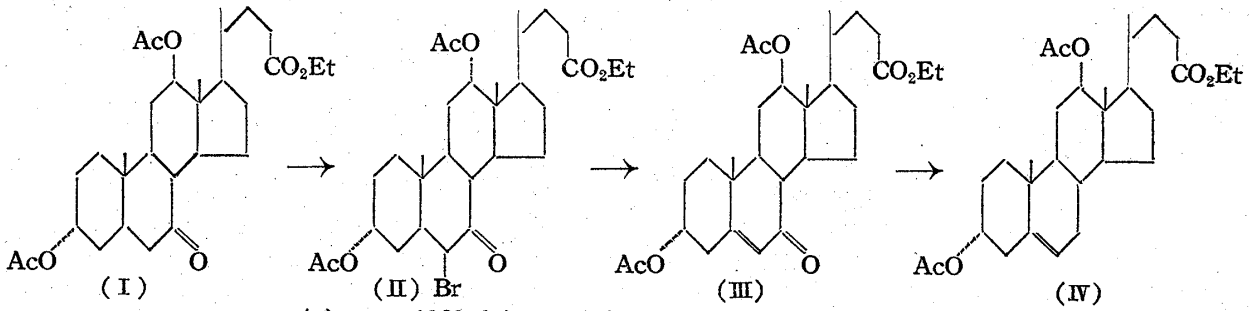
80. Ken'ichi Takeda, Kikuo Igarashi, and Taichiro Komeno : Bile Acids and Steroids. V.* Bromination of Methyl 3α-Acetoxy-7-oxocholanate and the Configuration of Bromine in the Related Compounds.

(*Research Laboratory, Shionogi & Co., Ltd.***)

In the third report of this series,[1] two monobromo compounds, (IIa), m.p. 136°, $[\alpha]_D$: +31.9°, and (IIb), m.p. 162°, $[\alpha]_D$: +34.6°, were shown as being obtained by the bromination of 3α,12α-diacetoxy-7-oxocholanic acid ester (I) in glacial acetic acid. Through dehydrobromination of these compounds by refluxing with pyridine-silver nitrate, two isomeric α,β-unsaturated ketones, (IIIa) and (IIIb), were formed. From these facts it was concluded that the two isomers, (IIa) and (IIb), were not epimers arising from the configuration of the bromine atom.



In the present paper, the results of similar investigations on methyl 3α-acetoxy-7-oxocholanate (V) are reported.

By the bromination of (V) in glacial acetic acid as in the previously described manner, two crystals were recognized by their melting points, (VIII), m.p. 176°, $[\alpha]_D$: +66.6°, and (VII), m.p. 167°, $[\alpha]_D$: −20.2°, and (VIII) was always obtained in a large yield than (VII). Analytical values showed that both were monobromo derivatives of (V). These two were synthesized also from the enol acetate of (V) according to the following procedures

* Part IV : Ann. Rept. Shionogi Lab., **4**, 43(1954).

** Imafuku, Amagasaki, Hyogo-ken (武田健一, 五十嵐喜九男, 米野太一郎).

1) K. Takeda, T. Komeno : J. Biochem. (Japan), **41**, 385(1954).