20. Shigehiko Sugasawa, Toshirō Fujisawa, and Kōzō Okada: Synthesis of 2,2′-Polymethylene-bis-(*Py*-tetrahydroisoquinoline) Derivatives. I. Synthesis of 2,2′-Ethylene-bis-(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline).†

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**, and *Research Laboratories of Institute of Pharmaceutical Resources***)

In his paper on the synthetic neuromuscular blocking agents, Taylor[1] described the preparation of more than twenty heterocyclic decamethylene-bis(quaternary ammonium salts), which were prepared according to two general methods: (i) An excess (usually 50%) of the appropriate tertiary amine refluxed with decamethylene dihalide in a neutral solvent such as benzene for, in general, 24~48 hours. (ii) A 200% excess of appropriate secondary amine refluxed with decamethylene dihalide in benzene solution yielded the corresponding bistertiary amine, from which the required bis(quaternary ammonium salt) was prepared by treating with an alkyl halide in ethereal or benzene solution. Laudolissin, prepared from papaverine and sebacic acid, is 2,2′-decamethylene-bis-laudanosinium halide and is reportedly a potential synthetic *d*-tubocurarine substitute of this kind.

In our effort to exploit the utilization of safrole, a superfluous material in our country, we intended to synthesize a series of ammonium salts of *Py*-tetrahydroisoquinoline derivatives mentioned in the title, in quest of new neuromuscular blocking agents.

6-Chloromethylsafrole prepared according to Ichikawa[2] by applying Blanc-Quelet reaction upon safrole, was dissolved in chloroform and was saturated with dry hydrogen bromide, giving 6-bromomethylsafrole (I), which turned into the hydrobromide on prolonged action of an excess of hydrobromic acid. The same compound was obtained, but in by far the inferior yield, when safrole hydrobromide[3] underwent the Blanc-Quelet type bromomethylation, which reaction, however, served to confirm the constitution of compound (II).

The action of primary amine upon (II) was then investigated and as a preliminary this was treated with aniline. A single substance was obtained in fair yield, which was found to be a tertiary and not a secondary base. Of the two possible formulae (III) (2-phenyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) and (IV) (di-1-(propenyl-4,5-methylenedioxybenzyl)-aniline) for this base, the former was found to be correct from its analyses and its indifference toward activated hydrogen.[4]

The action of ethylenediamine upon (II) proceeded in a similar way and 2,2′-ethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (V) was produced in even better yield. Its constitution was proved unequivocally by direct comparison with an authentic

---

* Hongo, Tokyo. (菅沢重彦). **Nukui, Koganei-machi, Kitatama-gun, Tokyo. (藤沢俊郎, 岡田光三).

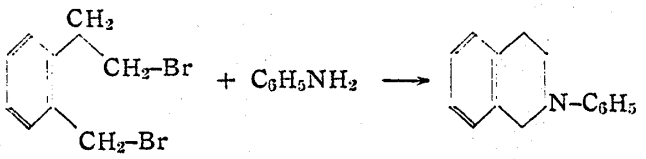
† Studies on the Utilization of Safrole as Medicinal Raw Materials. (VIII).

1) Taylor: J. Chem. Soc., 1951, 1150; *ibid.*, 1952, 142, 1309.

2) J. Chem. Soc. Japan, 71, 67 (1950).

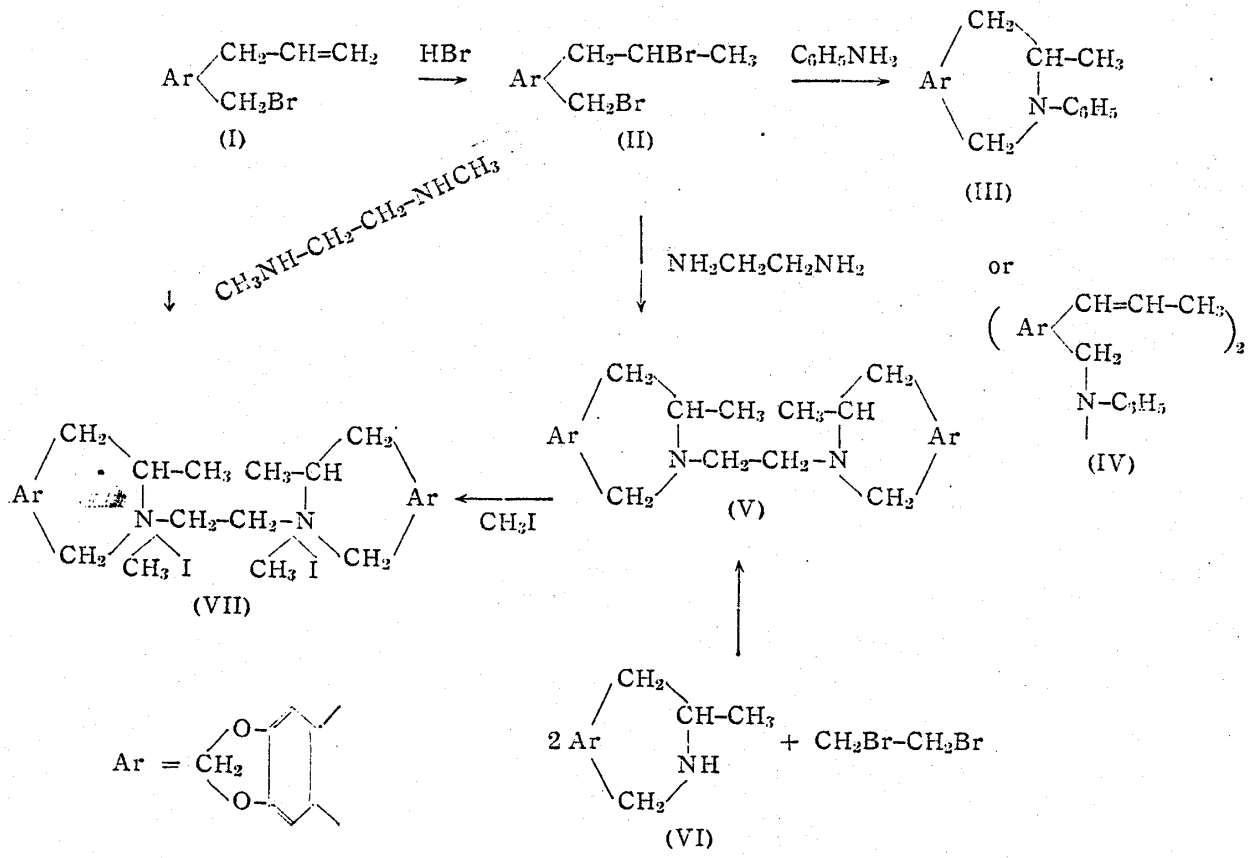
3) Orcutt: J. Am. Chem. Soc., 58, 2057 (1936).

4) von Braun (Ber., 56, 2142 (1923)); *cf.* also Holliman: J. Chem Soc., 1942, 737; 1945, 34) has already described a somewhat similar synthesis of 2-phenyl-*Py*-tetrahydroisoquinoline from *o*-β-bromoethylbenzyl bromide and aniline. But in his case, different from ours, both bromine atoms are primary and so there can hardly be any other compound than tetrahydroisoquinoline as the reaction product.



specimen, prepared by condensing 3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline(VI) with ethylene dibromide in benzene solution, which reaction required about 70 hours for its completion.

(V) gave the corresponding dimethiodide (VII), when treated with an excess of methyl iodide, which was also produced by heating (II) with N, N'-dimethylethylenediamine followed by potassium iodide.



(I) (II) (III) (IV) (V) (VI) (VII)

The synthesis of various other symmetrical polymethylene compounds as well as similarly constructed asymmetrical derivatives are now under progress and the results will be published in the forthcoming communication at a later date.

Our thanks are due to Messrs. Sekijima, Fukuda, Nara, Kaneko, and Sakai for microanalytical data.

Experimental

6-Bromomethylsafrole (I) — (i) 6-Chloromethylsafrole[2] (3 g.) in dry chloroform (30 cc.) was saturated with dry hydrogen bromide at around 5°. The excess of hydrogen bromide was now removed by introducing dry air stream through the solution and the whole was kept standing over night and then evaporated. Most of the residue solidified, when kept in an ice chest for about two days, which was separated and crystallized from petroleum ether, forming colorless needles of m.p. 57~58°; yield, 2 g. or 50%. *Anal.* Calcd. for $C_{11}H_{11}O_2Br$: Br, 31.3. Found: Br, 31.3.

(ii) Safrole (40.5 g.) in tetrachloroethane (80 cc.) was added with formalin (24 cc. of 30%) and freshly fused zinc chloride (2.5 g.). The mixture was saturated with dry hydrogen bromide at 0° to −7° with stirring, and the product was then poured on crushed ice (ca. 120 g.) while being stirred. Tetrachloroethane layer separated was washed twice with water, twice with 5% soda solution, and again twice with water free from acid and alkali. After being dried over sodium sulfate the solvent was distilled off, leaving dark colored oily residue, which appeared to be undistillable without decomposition even in high vacuum. Therefore, this was extracted with petroleum ether, filtered, and the solvent was evaporated. The residue was now fractionated in vac., giving

a fraction of b.p_{12} 165°, which solidified on standing and was purified from petroleum ether, forming colorless needles of m.p. 56~57°, alone or on admixture with the sample obtained above. Yield, 5%.

6-Bromomethylsafrole hydrobromide (II)—(i) 6-Chloromethylsafrole (10 g.) in pure chloroform (50 cc.) was saturated with dry hydrogen bromide at 5° and kept in an ice chest for 3 days in a well-stoppered bottle. The excess of hydrogen bromide was now removed by passing dry air stream, the solvent evaporated and the residue was fractionated. After some forerunner (b.p_5 110~123°, consisting mainly of (I)) the main fraction came over at 170~175° (5 mm.) in 50% yield (8 g.). *Anal.* Calcd. for $C_{11}H_{12}O_2Br_2$: Br, 47.6. Found: Br, 47.0.

(ii) Safrole hydrobromide[3] (24 g.) in dry tetrachloroethane (50 cc.) was added with formalin (10 cc. of 30%) and freshly fused zinc chloride (8 g.) and treated with dry hydrogen bromide according to the Blanc-Quelet method. The product was worked up as usual, giving (II), b.p_5 170~172°, in 10% yield (3.5 g.). Some of the starting material was recovered.

2-Phenyl-3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline (III)—(II) (0.7 g.) in pure benzene (10 cc.) was added with aniline (0.58 g. corresponding 3 moles ratio to II) in pure benzene (10 cc.) and the mixture was refluxed on a steam bath for about 2 hours and then kept standing over night. Aniline hydrobromide (0.56 g. or 76% of the theoretical amount) separated was filtered off and the filtrate was shaken repeatedly with enough dilute hydrochloric acid to extract basic substance. The aqueous acid solution was then basified with ammonia and the freed base was collected in ether, dried, and evaporated, leaving oily residue, in which the presence of both primary (aniline) and tertiary amines was indicated. On fractionation a fraction of b.p_8 195~198° was obtained in 45% yield (0.25 g.), which was proved to be saturated toward activated hydrogen and was characterized through its crystalline picrate and methiodide as (III).

Picrate. Yellow needles from alcohol, m.p. 142°(decomp. at 146°) *Anal.* Calcd. for $C_{23}H_{20}O_9N_4$: C, 55.6; H, 4.05; N, 11.3. Found: C, 56.1; H, 4.3; N, 11.6.

Methiodide. Yellow clusters from methanol, m.p. 221°(decomp.). *Anal.* Calcd. for $C_{18}H_{20}O_2NI$: N, 3.4; I, 31.0. Found: N, 3.55; I, 31.1.

2,2'-Ethylene-bis(3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline) (V)—(II) (2.24 g.) in pure benzene (30 cc.) was mixed with ethylenediamine (0.6 g.) in pure benzene (10 cc.) and the whole refluxed gently on a steam bath for ca. 5 hours and then left standing over night. Ethylenediamine hydrobromide, recovered in 93% yield (1.35 g.), was filtered off and the filtrate was extracted thoroughly with lukewarm dilute hydrochloric acid. The acid solution was then basified with ammonia and the base was collected in ether, washed, dried, and evaporated. The residue, 1.1 g. (or 84%), gradually solidified on standing and was purified from absolute ethanol, forming clusters of m.p. 146°. *Anal.* Calcd. for $C_{24}H_{28}O_4N_2$: C, 70.55; H. 6.9; N, 6.85; M, 408. Found: C, 70.7; H, 7.1; N, 6.95; M, 396 (Micro-Rast).

Hydrochloride. Colorless needles from 60% ethanol, m.p. 269°(decomp.). *Anal.* Calcd. for $C_{24}H_{30}O_4N_2Cl_2H_2O$ (dried at 50~60°, 8 mm.): C, 57.7; H, 6.65; N, 5.6. Found: C, 57.6; H, 6.6; N, 5.95.

Picrate. Yellow scales from glacial acetic acid, m.p. 211° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_4N_2 \cdot 2C_6H_3O_7N_3$: C, 49.9; H, 3.9; N, 12.9. Found: C, 4.8; H, 3.7; N, 12.4.

The same base was obtained when 3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline (VI)[5] (3.5 g.) in absolute benzene (24 cc.) was refluxed with ethylene dibromide (0.95 g.) for 70 hours. After removing (VI), hydrobromide separated, the filtrate was worked up as usual, giving crude (V), which was purified from absolute ethanol, forming colorless clusters of m.p. 146°, alone or admixed with the sample obtained above. Yield, 1.3 g. or 65%.

(V)-Dimethiodide (VII): (i) (V) was mixed with about 3 moles ratio of methyl iodide in methanol and the mixture was heated in a sealed tube at 100° for 2 hrs. Crystalline solid, which separated on cooling, was purified from aqueous ethanol, forming greenish yellow needles of m.p. 223° (decomp.). *Anal.* Calcd. for $C_{24}H_{28}O_4N_2 \cdot 2CH_3I \cdot 2H_2O$: C, 42.85; H, 5.2; N, 3.8. Found in subs. dried at 55~65° in vac.: C, 42.55; H, 5.3; N, 4.0.

(ii) 6-Bromomethylsafrole hydrobromide (II: 2.5 g.) in pure benzene (30 cc.) was mixed with N,N'-dimethylethylenediamine[6] (0.65 g.) dissolved in pure benzene (10 cc.), and the whole was refluxed gently on a steam bath for about 8 hrs., and was kept standing over night. Crystalline solid separated, which consisted of (V)-dimethobromide and (II)-dihydrobromide, was collected on a filter (2.7 g.) and was washed with cold water, leaving the former undissolved. This was then treated with potassium iodide in aqueous alcoholic solution, separating (VII) immediately, which was purified from aqueous alcohol, forming colorless minute needles of m.p. 223° (decomp.), and was proved to be identical with the substance obtained under (i).

The method (i) is preferable for the preparation of (VII).

---

5) Rosenmund: German Pat. 320,480 (Frdl., 13, 883).
6) J. Am. Chem. Soc., 74, 3933 (1952).

Summary

6-Bromomethylsafrole hydrobromide (II), prepared from safrole by the Quelet-reaction followed by HBr-treatment, was treated with aniline and ethylenediamine in boiling benzene solution, giving 2-phenyl-3-methyl-6,7-methylenedioxy-*Py*-tetrahydroisoquinoline (III) and 2,2′-ethylene-bis compound (V) in fair yields, respectively, as a single product, showing that tetrahydroisoquinoline formation is a general reaction, when (II) is treated with primary amine. Dimethiodide of (V) was also prepared.

(Received November 29, 1952)