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Summary

Re-esterification of sucrose monostearate at the condition similar to the alcoholysis reaction was investigated. Sucrose and sucrose polystearate, e.g., di- and tri-stearate, were produced as a result of re-esterification. It was concluded that the composition of the product gave a good accordance with the values calculated by the random distribution rule. Equilibrium was reached in about three hours.

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88. Goro Hayashi,[*1] Mikio Takeda,[*1] Hiroshi Kugita,[*1] Norio Sugimoto,[*1] and Hajime Fujimura[*2]: The Preparative and Pharmacological Studies of *levo* and *dextro* 9-Aza-des-N-morphinan (2,3,4,4*a*-Tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridin-9-ol).

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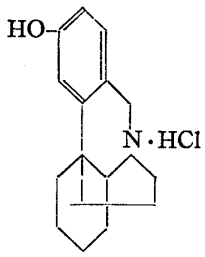
An isomer of morphinan, 9-aza-des-N-morphinan, DH-7 (2,3,4,4*a*-tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridin-9-ol) was first synthesized by Sugimoto, *et al.* in 1955.[1] In a recent communication[2] the pharmacological studies of this compound has been detailed by Fujimura, *et al.*



This paper concerns with the preparation and pharmacological evaluation of optical active forms of DH-7, the *dextro*-(DH-14) and *levo*-(DH-15) isomers.

Optical resolution

Direct resolution of the racemate (DH-7) with various optical acids were without success. Efforts were then turned to the resolution of (±)-3-methoxy-9-aza-des-N-morphinan, a prior compound of DH-7. *d*-Tartaric acid formed crystalline salts with the optical isomers of the methoxy compound, which upon recrystallization separated the salt of the *dextro*-isomer. Crude salt of the *levo*-isomer from the mother liquor could not be purified by recrystallization. Conversion of the crude salt to free base and in turn to the *d*-camphor-*β*-sulfonate afforded a well-defined salt of the *levo*-isomer. One-step separation of the *levo*-isomer from the racemate with *d*-camphor-*β*-sulfonic acid was unsuccessful.

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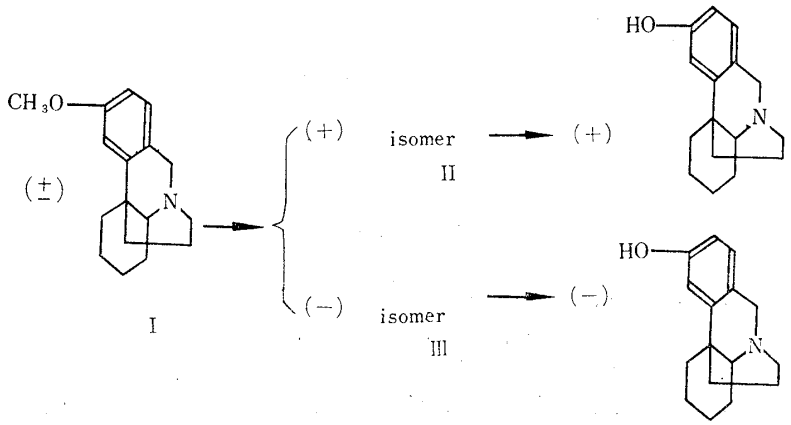
1) N. Sugimoto, H. Kugita: This Bulletin, **3**, 11 (1955).
2) H. Fujimura, N. Sugimoto, G. Hayashi: Japanese J. Pharmacol., **11**, 101 (1962).



The optical isomers of the methoxy compound were respectively hydrolized with hydrobromic acid to the *dextro*- and *leve*-hydroxy compound.

Experimental

Resolution of (±) 3-Methoxy-9-aza-des-N-morphinan (9-Methoxy-2,3,4,4*a*-tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridine)——A mixture of 2.9 g. of (±) 3-Methoxy derivative (I), 1.8 g. *d*-tartaric acid and 4 cc. of water was heated in a water bath to a clear solution and concentrated to dryness under reduced pressure. The crystalline residue was recrystallized twice from 90% EtOH to give 1.75 g. of colorless rectangles of (+)-isomer *d*-tartarate, m.p. 198～199°(decomp.). *Anal.* Calcd. for $C_{21}H_{29}O_7N$: C, 61.90; H, 7.17; N, 3.44. Found : C, 61.98; H, 6.88; N, 3.9. 1.65 g. of the *d*-tartarate was dissolved in water, basified with NH_4OH, extracted with Et_2O, dried and evaporated. Distillation of the residue gave 0.87 g. of (+) 3-methoxy-9-aza-des-N-morphinan (II) as colorless oil, b.$p_{0.4}$ 145～147°, $[\alpha]_D^{20}$ +16.7° (c=1, EtOH).

Mother liquors of the above recrystallization were combined and concentrated to dryness, the residue was dissolved in water, basified with NH_4OH, extracted with Et_2O, dried and evaporated. A mixture of 1.7 g. of the recovered free base and 1.6 g. of *d*-camphor-*β*-sulfonic acid were dissolved in 5 cc. of EtOH. EtOH was distilled and the crystalline residue was recrystallized twice from EtOH-Et_2O to give 1.9 g. of colorless plates, m.p. 185～187°(decomp.). *Anal.* Calcd. for $C_{27}H_{39}O_5NS$: C, 66.23; H, 8.03; N, 2.86. Found : C, 66.08; H, 7.66; N, 3.04.

0.98 g. of the (−)-isomer (III) was obtained from the salt as colorless oil, b.$p_{0.4}$ 145°, $[\alpha]_D^{20}$ −15.0 (c=1, EtOH).

(+) 3-Hydroxy-9-aza-des-N-morphinan(DH-14)(2,3,4,4*a*-Tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridin-9-ol)——0.7 g. of the (+) 3-methoxy derivative was heated with 7 cc. of 48% HBr for 2.5 hr. HBr was distilled under reduced pressure, the residue was dissolved in 12 cc. of water, basified with conc. NH_4OH and filtered. Recrystallization from AcOEt gave 0.51 g. of colorless feather-like needles, m.p. 244～246°(decomp.), $[\alpha]_D^{20}$ +26.3°(c=0.8, EtOH). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76. Found : C, 78.71; H, 8.65; N, 5.44.

(−) 3-Hydroxy-9-aza-des-N-morphinan(DH-15)(2,3,4,4*a*-Tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridin-9-ol)——The (−) 3-methoxy derivative (0.96 g.) was hydrolyzed as the above. 0.64 g. of colorless feather-like needles was obtained from AcOEt, m.p. 244～246°(decomp.), $[\alpha]_D^{20}$ −25.5°(c=0.8, EtOH). *Anal.* Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.76. Found : C, 79.0; H, 8.66; N, 6.02.

Pharmacological Results——1) Analgesic Activity and Acute Toxicity in Mice : Analgesic activity in mice was measured by the hot-plate method[3] and Haffner's method.[4] All compounds were administered subcutaneously.

The analgesic potency of *levo*-isomer (DH-15) was about two times as active as that of racemate (DH-7), while the *dextro*-isomer (DH-14) was inactive (Table I).

2) Effect of Threshold Dose of Morphine on the Analgesic Activity of DH-15 in Mice : In order to see whether DH-15 is potentiative with additive to morphine, subcutaneous ED_{50} was determined for DH-15 and morphine respectively with the subcutaneous threshold dose of morphine (4 mg./kg.) administered simultaneously at a separate part of the skin.

As shown in Table II, the marked potentiating effect by morphine was observed on DH-15, while no synergistic activity was observed on DH-14.

3) N. B. Eddy, D. Leimbach : J. Pharmacol. Exptl. Therap., **107**, 385 (1953).
4) F. Haffner : Deutsch. Med. Wochr., **55**, 731 (1929).

Table I. Analgesic activity and Acute Toxicity in Mice

Compound	Toxicity s.c. (LD_{50} mg./kg.)	Analgesic activity (ED_{50} mg./kg. s.c.) Hot-plate	Haffner
DH-7·HCl	35.4 (26.6～47.2)	9.15 (6.1～13.6)	16.60 (97.～26.8)
DH-14·HCl	67.7 (55.3～72.2)	none	none
DH-15·HCl	40.7 (30.5～54.3)	4.28 (3.3～5.5)	9.16 (5.0～15.6)
morphine·HCl	350.3 (337.0～585.2)	6.81 (4.6～9.8)	9.46 (5.4～16.0)

( ): 95% confidence limit.
ED_{50} and LD_{50} were calculated by the Weil's method[5]

Table II. Analgesic activity of DH-15 and Morphine in Combined Administration of Threshold-Dose of Morphine by the Haffner's method

	ED_{50} mg./kg. (alone)	ED_{50} mg./kg. (with morphine 4 mg./kg.)
DH-15·HCl	9.16 (5.0～15.6)	1.54 (0.53～2.56)
morphine·HCl	9.46 (5.4～16.0)	5.46 (3.66～8.88)

( ): 95% confidence limit.

3) Antagonism of Levallorphane to DH-15 : DH-15 and morphine were administered subcutaneously 20 minutes after the subcutaneous injection of Levallorphane and analgesic activity was evaluated by the hot-plate method.

The analgesic action of morphine was completely antagonized even with 1 mg./kg. of Levallorphane, while the weak analgesic effect was found for DH-15 and this effect was almost completely antagonized with 2 mg./kg. or more of Levallorphane.

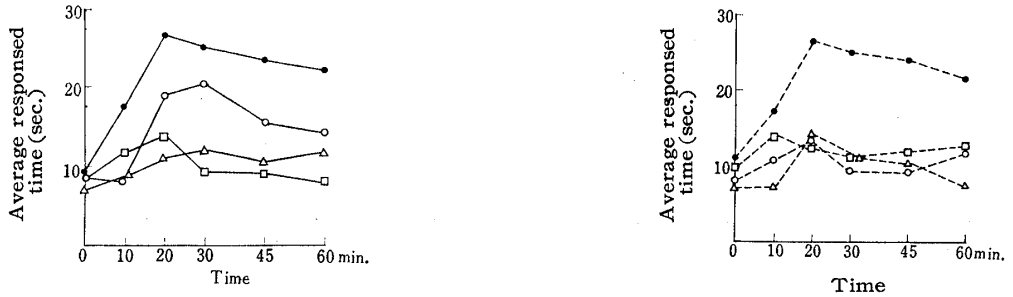
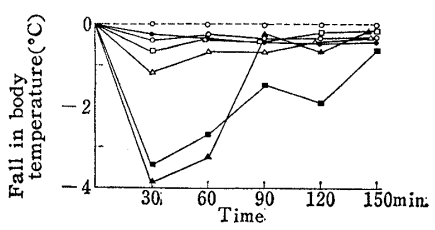


Fig. 1. Effect of Levallorphane on the Analgesic Effect of DH-15 and Morphine

—•— DH-15 9 mg./kg.
—○— DH-15 9 mg./kg.+Levall. 1 mg./kg.
—△— DH-15 9 mg./kg.+Levall. 2 mg./kg.
—□— DH-15 9 mg./kg.+Levall. 4 mg./kg.
····•···· morphine 10 mg./kg.
····○···· morphine 10 mg./kg.+Levall. 1 mg./kg.
····△···· morphine 10 mg./kg.+Levall. 2 mg./kg.
····□···· morphine 10 mg./kg.+Levall. 4 mg./kg.

Mean for groups of ten mice represented by vertical line

4) Effect on Body Temperature of Mice and Rats : a) Mice—The subcutaneous injection of DH-15 caused a hypothermic effect like that of morphine, but its effect was shorter than that of morphine. No significant effect on body temperature was found for DH-14.



····○···· control
—○— DH-14 6 mg./kg.
—•— DH-14 12 mg./kg.
—□— morphine 6 mg./kg.
—■— morphine 12 mg./kg.
—△— DH-15 6 mg./kg.
—▲— DH-15 12 mg./kg.

The curves indicate average of five mice

Fig. 2. Effect of DH-14, DH-15, and Morphine on the Body Temperature of Mice (subcutaneous injection)

5) C.S. Weil. : J. Biometric Society, 8, 249 (1952).

b) Rats—DH-15 caused a rise in rectal temperature of rats after subcutaneous injection, though the action was somewhat weaker than morphine. 12 mg./kg. of DH-14 produced a slight rise of the temperature.

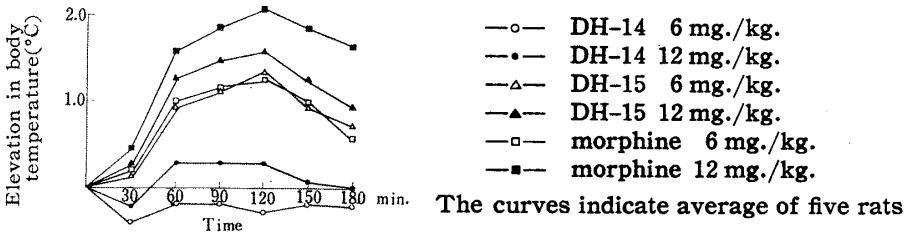


Fig. 3. Effect of DH-14, DH-15, and Morphine on the Body Temperature of Rats (subcutaneous injection)

5) Augmentation of the Effect of Barbiturate : Male *dd*-strain mice weighing 15~18 g. were injected subcutaneously with the compounds. Twenty minutes later, 25 mg./kg. of sodium thiopental was administered intravenously at the rate of 0.15 ml./sec./15 g. of body weight and the duration of loss of the righting reflex were measured.

DH-14 caused no effect on the sleeping time of mice injected with the barbiturate, while DH-15 showed same remarkable augmentation of the effect of barbiturate as that of morphine.

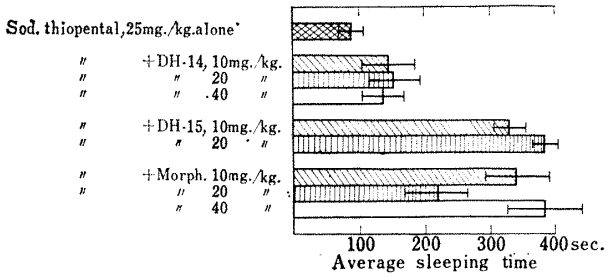


Fig. 4. Augmentation of the Effect of Barbiturate, Means for group of five mice

6) Effect on the Pupil of Mice : The method described by Pulewka[6] was used. DH-14 and DH-15 administered subcutaneously at a dose of 6~12 mg./kg. did not produced the mydriatic response caused by morphine. DH-14 produced miosis rather than mydriasis.

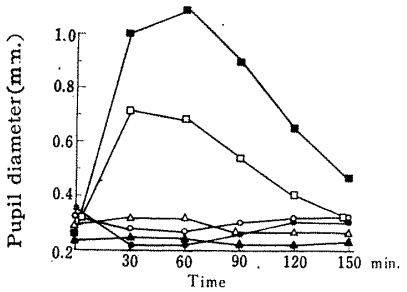


Fig. 5. Effect on the Pupil of Mice, Means for groups of five mice

—o— DH-14 6 mg./kg.
—•— DH-14 12 mg./kg.
—△— DH-15 6 mg./kg.
—▲— DH-15 12 mg./kg.
—□— morphine 6 mg./kg.
—■— morphine 12 mg./kg.

7) Effect on the Gastrointestinal Propulsion : A group of ten male *dd*-strain mice, fasted for 24 hr. befor experiment, were injected subcutaneously with aqueous solution of the test compounds. Fifteen minutes later, the mice were given orally 0.3 ml. ofan aqueous suspension of charocoal (charcoal-carboxymethylcellulose-water=10: 0.5:100). Twenty minutes after charcoal meal the mice were killed by a blow on the head, the intestines was excised and the propulsive rate of the charcoal to the whole length of the small intestine was measured.

DH-15 inhibited the gastrointestinal propulsion of the charcoal meal, but its effect was weaker than that of morphine. The effect of DH-14 was the weakest in the compounds tested.

6) Pulewka : Arch. exp. Path. Pharmak., **168**, 307 (1932).

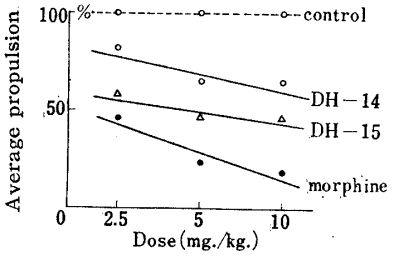


Fig. 6. Effect on the Gastrointestinal Propulsion, One group of ten Mice

The percentage was the propulsive rate of the group injected with test compound to the control group injected with saline.

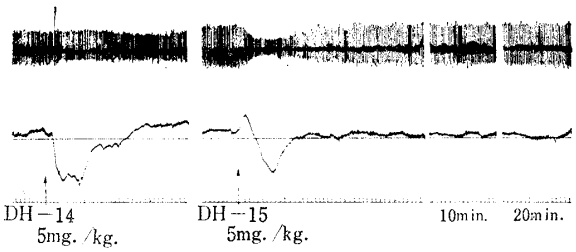


Fig. 7. Effect on Blood Pressure and Respiration of Urethane Anaesthetized Rabbit

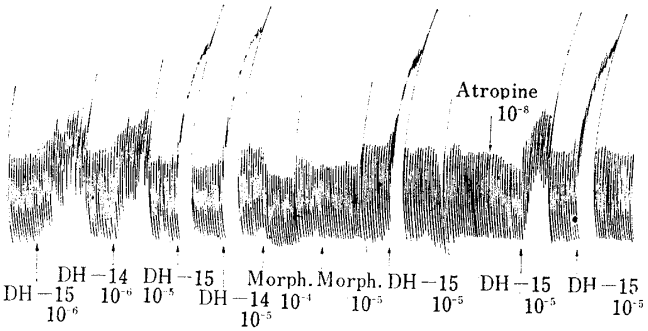


Fig. 8. Effect on isolated small Intestine of Rabbit

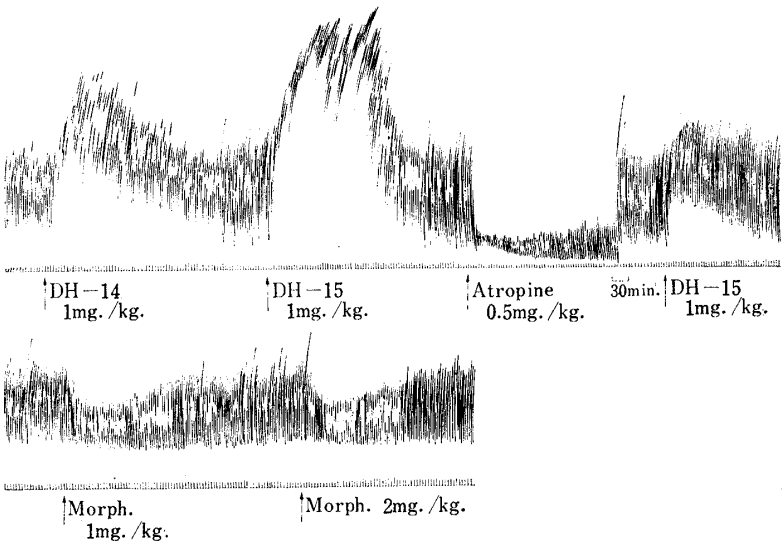


Fig. 9. Effect on small Intestine of Urethane Anaesthetized Rabbit

Movement of small intestine were recorded by means of Trendelenburg's method modified by Nuki.

8) Effect on the Blood Pressure and Respiration in Rabbits : Intravenous injection of DH-14 and DH-15 caused temporary depression of the depth of respiration and increared respiratory frequency in the dose more than 2 mg./kg. Five milligrams per kilogram of both compounds produced a fall carotid blood pressure and a respiratory depression Fig. 7.

9) Effect on the Intestine of Rabbits : The methods used to record movements of intestine were that described by Magnus in isolated intestine and by Nuki *in vivo*. *In vivo* experiments rabbits were anaesthetized with 0.8 g./kg. of urethane.

As shown in Fig. 8 and Fig. 9, morphine reduction of the amplitude of spontaneous contraction and decreased tonus, but DH-14 and DH-15 produced the contraction of isolated intestine in the concentration of more than 1 μg./ml.

Same results were obtained *in vivo* experiments by the intravenous administration of the dose more than 0.5 mg./kg. The effects of DH-14 and DH-15 were antagonized by atropine in both experiments.

Discussion

The marked analgesic effect was found in *levo* isomer (DH-15) of racemate (DH-7), but not in *dextro* isomer (DH-14). These facts suggest that the correlation between optical configuration and analgesic effect in these compounds is similar to that of morphine. Central actions, such effects as on pain, on body temperature, on barbiturate anesthesia etc., were not exhibited by DH-14. But DH-15 produced the central actions similar to morphine. On the small intestine of rabbits, however, the actions of DH-14 and DH-15 were contrary to morphine; while morphine reduced the spontaneous contraction and tonus of the small intestine, DH-14 and DH-15 produced a marked contruction which was antagonized by atropine. This shows that effect of DH-14 and DH-15 were cholinergic. Although DH-14 had not analgesic effect, it showed the peripheral side action as strong as DH-15.

Therefore the compound with more active analgesic action and less side effect could be obtained by the preparation of *levo* isomer from racemate.

Summary

The analgesic effect was found in *levo*-isomer (DH-15) of 2,3,4,4*a*-tetrahydro-1*H*,6*H*-5,10*b*-propanophenanthridin-9-ol, but not in *dextro*-isomer (DH-14).

The analgesic effect of DH-15 was some what stronger than morphine, synergistic to morphine and antagonized by Levallorphane. The acute toxicity of DH-15 was far stronger than that of morphine.

The pharmacological effects of DH-15 on the body temperature of mice and rats, barbiturate anaesthesia in mice, purpil of mice and gastrointestinal propulsion in mice were similar to that of morphine, but less active except barbiturate anaesthesia. DH-14 showed little effects.

The contraction or increase of tonus in the isolated or *in situ* intestine of rabbits by the low dosis of DH-14 and DH-15 were observed.

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