1.90, Ala 2.73, Leu 0.78 (average recovery 89%). Amino acid ratios in Ap-M digest (theory is given in parenthesis): Ser+Asn 3.37 (4 calcd. as Ser), Tyr 2.32 (2), Met 1.01 (1), Glu 5.44 (5), His 0.76 (1), Phe 3.00 (3), Arg 3.17 (3), Trp 0.91 (1), Gly 2.98 (3), Lys 4.06 (4), Pro 4.04 (4), Val 3.30 (3), Asp 0.65 (1), Ala 2.98 (3), Leu 1.06 (1) (average recovery 77%). *Anal.* Calcd. for $C_{207}H_{308}O_{58}N_{56}$–$8CH_3COOH \cdot 14H_2O$: C, 50.78; H, 7.03; N, 14.87. Found: C, 50.75; H, 6.61; N, 14.73.

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Studies on the Syntheses of Analgesics. XLI.[1] Optical Resolution of (±)-N-Cyclopropylmethyl-3-hydroxy-9-azamorphinan (Studies on the Syntheses of Heterocyclic Compounds. Part DCLXIX[2])

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Optical resolution of (+)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan (I) was successfully effected with (+)-*O*,*O*-dibenzoyltartaric acid or (2*R*: 3*R*)-2′-nitrotartranilic acid as the resolution agent. The optically active compounds thus obtained were tested for their analgesic activity and antagonistic effect of morphine analgesia.

Previously, we reported the several synthetic methods of the 9-azamorphinan ring system[4] and found this type of compounds to have an analgesic activity. Especially, the title compound *N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan (I) was found to be about twice as potent as pentazocine in the analgesic activity, but to show no side effects such as addiction.[4d] Therefore, we have examined the pharmacological activity of the optically active compound of I and attempted to accomplish the optical resolution of I. Here we wish to report the successful resolution of I and also the analgesic activity of the optically active compounds.

Firstly, we investigated the optical resolution of compounds (I—III) in several solvents by using (+)-*O*,*O*-dibenzoyltartaric acid,[5] which was widely used as a resolution agent in morphinan system compounds, and (2*R*: 3*R*)-2′-nitrotartranilic acid,[6] which was developed as an effective resolution agent by Montzka, Pindell and Matiskella.[6] Both of them effected successfully the resolution of I in 2-propanol and in 90% ethanol while cooling in refrigerator to give the crystalline salt of optically active isomer. Furthermore, (+)-binaphthylphosphoric

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3) Location: *a) Aobayama, Sendai*; *b) Sakurashinmachi-2-chome, Setagaya-ku, Tokyo.*
4) *a*) T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, *Chem. Pharm. Bull.* (Tokyo), **16**, 296 (1968); *b*) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, and N. Wagatsuma, *Chem. Pharm. Bull.* (Tokyo), **17**, 1096 (1969); *c*) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, N. Wagatsuma, F. Satoh, and S. Saito, *J. Med. Chem.*, **13**, 1064 (1970); *d*) T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Uryu, and K. Araki, *J. Med. Chem.*, **16**, 301 (1973).
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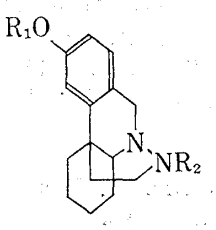

I: R_1=H, R_2=CH_2- 

II: R_1=$COCH_3$, R_2=CH_2- 

III: R_1=$CH_2C_6H_5$, R_2=CH_2- 

IV: R_1=R_2=H

V: R_1=R_2=CO-

Chart 1

acid[7] was used as the resolution agent, but gave the negative result. The optical rotation of (+)-isomer and (−)-isomer of the compound I were each $[\alpha]_D^{27}$: +101.6° and $[\alpha]_D^{27}$: −102.4°, respectively.

Similarly, 3-hydroxy-9-azamorphinan (IV)[4c] was resolved with this reagent to give the optically active compounds, (+)-IV, $[\alpha]_D^{26}$: +34.0° and (−)-IV, $[\alpha]_D^{26}$: −34.0°. (+)-3-Hydroxy-9-azamorphinan[(+)-IV] was subjected to a Schotten-Baumann reaction with cyclopropylcarbonyl chloride and the resulting *N*-acylated compound [(+)-V] was reduced with lithium aluminum hydride to give (+)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan[(+)-I], which was identical with the sample prepared by direct resolution of I in the comparisons of infrared (IR) spectrum and optical rotation.

Pharmacology

Table I showed the results of screening for the analgesic activities of the racemate and the optically active compounds of I by the acetic acid (intraperitoneal injection of 0.1 ml/10 g body weight of 1.0% acetic acid) induced stretching method.[8]

Male albino mice dd strain (18.0—22.0 g) were used. After these compounds were administered subcutaneously to five groups of animals consisting of ten mice per group, the effective ratio until 60 min was examined and effective dose 50% (ED_{50}) was calculated by the Lichfield-Wilcoxone method.[9]

Table I. Effective Ratio and ED_{50} by Lichfield-Wilcoxone Method

Method	Compd	ED_{50}, mean value mg/kg	95% fiducial limit mg/kg
Stretching	(±)—I	1.63	0.99—2.7
	(+)—I	*ca.* 80	
	(−)—I	0.45	0.22—0.91
	Pentazocine	2.40	1.56—3.70

An antagonistic effect of morphine analgesia (effective dose 100% (ED_{100}), 16 mg/kg, *sc.*) was calculated by Haffner method,[10] in which ten male mice dd strain per group were used and the results were summarized in Table II.

Table II. Comparison of the Antagonistic Effect of Morphine Analgesia by Haffner Method

Compd.	AD_{50} mg/kg, *sc.*	95% fiducial limit mg/kg
(±)—I	4.70	4.55—4.87
(+)—I	20	
(−)—I	2.20	1.80—3.30
Levallorphan	0.24	0.16—0.36

7) J. Jacques, C. Fouqdey, and R. Viterbo, *Tetrahedron Letters*, **1971**, 4617.
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9) J.T. Lichfield and F. Wilcoxone, *J. Pharmacol.*, **96**, 99 (1949).
10) F. Haffner, *Deut. Med. Wochenschr.*, **55**, 731 (1929).

As shown in the above Tables, (−)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan-[(−)-I]showed more effective analgesic activity and also antagonistic effect of morphine than the parent (±)-compound[(±)-I].

Experimental[11]

Optical Resolution of (±)-*N*-Cyclopropylmethyl-3-hydroxy-9-azamorphinan (I)——a) A solution of 2.0 g of (±)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan (I) and 2.4 g of (+)-*O*,*O*-dibenzoyltartaric acid[5] in 300 ml of acetone was left at room temperature overnight. The separated oil was washed with ether and crystallized from 2-propanol while cooling in refrigerator. The crystals were separated and recrystallized from 2-propanol to give 2.0 g of (−)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(−)-I](+)-*O*,*O*-dibenzoyltartrate as colorless needles, mp 158—160°. *Anal.* Calcd. for $C_{37}H_{40}O_9N_2 \cdot 1/2H_2O$: C, 66.75; H, 6.21; N, 4.21. Found: C, 67.09; H, 6.71; N, 4.02.

The above salt was treated with 28% NH_4OH and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 0.9 g (90%) of (−)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(−)-I] as colorless needles, mp 151—153° (from ether); $[\alpha]_D^{27}$: −102.4° (c=0.025, MeOH, l=0.1 dm). *Anal.* Calcd. for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.68; H, 8.97; N, 9.08.

The mother liquor from the above salt formation was concentrated to dryness. The residue was basified with 28% NH_4OH and extracted with ether. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a crystalline residue, which was recrystallized from ether to give 0.76 g (76.0%) of (+)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(+)-I] as colorless needles, mp 151—153°; $[\alpha]_D^{27}$: +101.6° (c=0.025, MeOH, l=0.1 dm). *Anal.* Calcd. for $C_{19}H_{26}ON_2$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.70; H, 9.04; N, 9.04.

b) A solution of 3.0 g of (±)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan (I) and 1.36 g of (2*R*: 3*R*)-2′-nitrotartranilic acid in 50 ml of 90% EtOH was heated in order to dissolve the undissolved material on a water bath and the resulting clear solution was set aside in refrigerator overnight. The separated yellow crystals were filtered and basified with 28% NH_4OH, a solution of which was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to give 0.5 g (33.3%) of (+)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(+)-I] as colorless needles, mp 151—153° (from ether), which was identical with the authentic sample from a) in comparisons of mp, IR spectrum and optical rotation.

To the mother liquor in the above salt formation 0.6 g of (2*R*: 3*R*)-2′-nitrotartranilic acid was added and the separated solid was filtered off. The filtrate was condensed to leave a residue which was dissolved in chloroform. The chloroform solution was washed with water, dried over $MgSO_4$, and evaporated to afford 0.7 g (43.3%) of (−)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(−)-I] as colorless needles, mp 151—153° (from ether), which was identical with the authentic sample from a) in comparisons of mp, IR spectrum and optical rotation.

Optical Resolution of (±)-3-Hydroxy-9-azamorphinan (IV)——A solution of 3.0 g of (±)-3-hydroxy-9-azamorphinan (IV) and 1.7 g of (2*R*: 3*R*)-2′-nitrotartranilic acid in 50 ml of 90% EtOH was heated in order to dissolve the undissolved material and the resulting clear solution was set aside overnight in refrigerator. The separated substance was collected by filtration and 2.2 g of the resulting yellow crystals were basified with 28% NH_4OH and extracted with chloroform. The extract was washed with water, dried over $MgSO_4$ and evaporated to afford 1.0 g (66.7%) of (+)-3-hydroxy-9-azamorphinan [(+)-IV] as colorless needles, mp 244—246° (from 2-propanol); $[\alpha]_D^{26}$: +34.0° (c=0.01, DMF, l=0.1 dm). *Anal.* Calcd. for $C_{15}H_{20}ON_2$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.98; H, 8.29; N, 11.36.

To the mother liquor in the above salt formation 0.3 g of (2*R*: 3*R*)-2′-nitrotartranilic acid was added and the separated solid was filtered off. The solvent was removed by evaporation of the above filtrate and the residue was dissolved in chloroform. The organic layer was washed with 10% NH_4OH and then water, dried over $MgSO_4$, and evaporated to give 1.2 g (80.0%) of (−)-3-hydroxy-9-azamorphinan [(−)-IV] as colorless needles, mp 244—246° (from 2-propanol); $[\alpha]_D^{26}$ −34.0° (c=0.01, DMF, d=0.1 dm). *Anal.* Calcd. for $C_{15}H_{20}ON_2$: C, 73.73; H, 8.25; N, 11.47. Found: C, 74.00; H, 8.35; N, 11.25.

(+)-*N*-Cyclopropylmethyl-3-hydroxy-9-azamorphinan [(+)-I]——To a suspension of 0.6 g of (+)-3-hydroxy-9-azamorphinan [(+)-IV] in 50 ml of ether and 20 ml of 10% NaOH solution was added 1.0 g of cyclopropylcarbonyl chloride with stirring at room temperature. After stirring for 1 hr, the organic layer was washed with 10% NaOH solution and then water, dried over K_2CO_3, and evaporated to give an oil, which was triturated with ether-pet. ether to form a solid. Recrystallization of this from ether afforded 0.5 g (53.5%) of (+)-*N*-cyclopropylcarbonyl-3-cyclopropylcarbonyloxy-9-azamorphinan (V) as colorless plates, mp 144—145.5°. *Anal.* Calcd. for $C_{23}H_{28}O_3N_2$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.47; H, 7.48; N, 7.85.

A mixture of 0.4 g of this amide (V) and 0.3 g of lithium aluminum hydride in 50 ml of dry dioxane was refluxed for 6 hr, and the excess of lithium aluminum hydride was decomposed with water. After separation

11) All melting points were measured in capillary tubes in a sulfuric acid bath and are uncorrected. Optical rotations were taken on JASCO-DIP-4 automatic polarimeter.

of an inorganic material, the filtrate was dried over $MgSO_4$ and evaporated to give 0.25 g (79.7%) of (+)-*N*-cyclopropylmethyl-3-hydroxy-9-azamorphinan [(+)-I] as colorless needles, mp 151—153° (from ether), which was identical with the authentic sample in comparisons of mp, IR spectrum and optical rotation.

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Studies on Prostaglandins. I. The Resolution of *dl*-(2β-Benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic Acid using L-Arginine[1]

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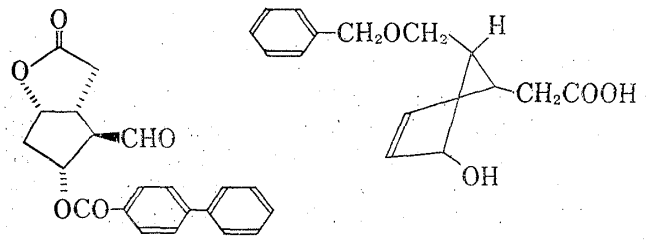
d-(2β-Benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic acid (*d*-II) which was a very important key intermediate for the synthesis of prostaglandins by a Corey's method was obtained by resolution of *dl*-II using L-arginine in a mixture of water and acetone.

A Corey's method[3] is the most important and useful method for the synthesis of natural prostaglandins (PGs) and their analogues. The key intermediate of the Corey's method is *d*-4β-formyl-2-oxo-5α-*p*-phenylbenzoyloxy-2,3,3aα,4α,5β,6aα-hexahydro-2H-cyclopenta[*b*]furan (I).[3e-g] I was synthesized using *d*-(2β-benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)-acetic acid (*d*-II) which was prepared by resolution of *dl*-II.[3g] Therefore the resolution of *dl*-II is the very important problem on the synthesis of PGs and their analogues by the Corey's method. Several resolving methods have been proposed.[3a,4-6] However, most of these methods not only used *d*-amphetamine as a resolving agent



l-I II(*d*,*l*,*dl*)

Chart 1

1) This study was presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975.
2) Location: *No. 1-8, Azusawa-1-chome, Itabashi-ku, Tokyo.*
3) *a*) E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969); *b*) E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker, and N.M. Weinshenker, *ibid.*, **92**, 397 (1970); *c*) E.J. Corey, R. Noyori, and T.K. Schaaf, *ibid.*, **92**, 2586 (1970); *d*) E.J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971); *e*) E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T.K. Schaaf, *ibid.*, **93**, 1490 (1971); *f*) E.J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971); *g*) E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, and R.K. Varma, *ibid.*, **93**, 1491 (1971).
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