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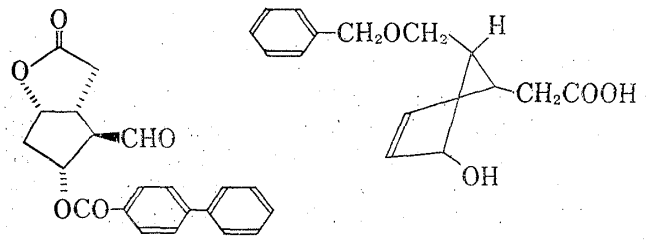
d-(2β-Benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic acid (*d*-II) which was a very important key intermediate for the synthesis of prostaglandins by a Corey's method was obtained by resolution of *dl*-II using L-arginine in a mixture of water and acetone.

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).
4) Schering A.-G., Ger. Offen 2215197 (1973) [*C.A.*, **80**, 14644*b* (1974)].
5) *a*) Pfizer Inc., Ger. Offen 2246408 (1973); *b*) *ibid.*, Japan Kokai 29345 (1972); *ibid.*, U.S. Patent 3873605 (1975).
6) *a*) Carllo Erba, S.P.A., Japan Kokai 67257 (1973); *b*) Chinoin Gyogyszer es Vegyeszeti Termekek Gyara Rt., Hung. Teljes 9419 (1975) [*C. A.*, **83**, 178425*u* (1975)].

whose use was strictly inhibited as an awakening drug, but also required complicated conditions. Besides the resolving yields of these methods were low.

We have been studied also on the resolving methods for *dl*-II and found a very simple and useful method using L-arginine. Namely, when a mixture of *dl*-II and one equimolar amount of L-arginine in acetone–water (6—7: 1) was allowed to stand at room temperature overnight, *d*-II·L-arginine salt was easily precipitated with 88—90% of a theoretical yield. Optical purity of the crystals thus obtained was very high and the recrystallization was scarcely needed: mp 197—200°; $[\alpha]_D^{25}$ +12.6° (c=1.4, water).[5] $[\alpha]_D^{25}$ of free acid (*d*-II) was +5.4° (c=1.8, methanol). *d*-II thus obtained was used for the synthesis of natural PGs and their analogues. On the other hand, *l*-II·L-arginine salt was obtained by concentration of the mother liquor followed by recrystallization of the residual crystals from methanol-acetone: mp 161—164°; $[\alpha]_D^{25}$ −0.6° (c=2.3, water). $[\alpha]_D^{25}$ of free acid (*l*-II) was −4.2° (c=1.6, methanol). *l*-II thus obtained was able to be used the synthesis of *ent*-11,15-*epi*-PGs.[7]

Experimental[8]

The Resolution of *dl*-(2β-Benzyloxymethyl-3α-hydroxy-4-cyclopenten-1α-yl)acetic Acid——A solution of *dl*-II (341 g, 1.3 mole) in acetone (500 ml) was mixed with a solution of L-arginine (226 g, 1.3 mole) in water (900 ml). To the mixture, acetone (about 2.5 liter) was added until the mixture became turbid. The mixture was allowed to stand overnight at room temperature and the precipitated white prism crystals (*d*-II·L-arginine salt) were collected by filtration and washed with acetone: weight 250 g (88.4% of a theoretical yield); mp 197—200°; $[\alpha]_D^{25}$ +12.6° (c 1.4, water). $[\alpha]_D^{25}$ of the free acid (*d*-II) was +5.4° (c 1.8, methanol) (*lit.*,[5] $[\alpha]_D^{25}$ +5.6° (c 1, methanol)). *Anal.* Calcd. for $C_{21}H_{32}O_6N_4$: C, 57.78; H, 7.39; N, 12.84. Found: C, 57.51; H, 7.50; N, 13.50.

The filtrate was concentrated under reduced pressure and the crystalline residue was recrystallized from a mixture of methanolacetone. 146 g of the needle crystals of *l*-II·L-arginine salt was obtained: mp 162—164°; $[\alpha]_D^{25}$ −0.6° (c 2.3, water), −2.31° (c 1.3, methanol). $[\alpha]_D^{25}$ of the free acid (*l*-II) was −4.2° (c 1.6, methanol). *Anal.* Calcd. for $C_{21}H_{32}O_6N_4$: C, 57.78; H, 7.39; N, 12.84. Found: C, 57.64; H, 7.58; N, 12.63.

7) E.J. Corey, S. Terashima, P.W. Ramwell, R. Jessup, N.M. Weinshenker, D.M. Floyd, and G.A. Crosby *J. Org. Chem.*, **37**, 3043 (1972).

8) All melting points are not corrected.