Arch. Pharm. Res. 10(1), 25-28 (1987)

The Absolute Configuration of Ketoprofen

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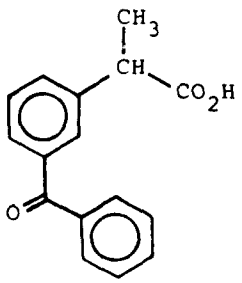
(Received February 20, 1987)

Abstract □(+)-Ketoprofen was obtained from resolution with (*S*)(+)-2-amino-1-butanol and its absolute configuration was determined to be (*S*) by chemical correlation with (*S*)(+)-ethyl hydratropate using Beckmann rearrangement as a key step.

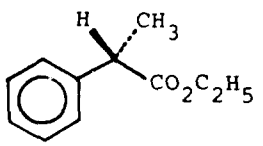
Keywords □ Arylpropionic acid, chemical correlation, Beckmann rearrangement, geometrical diastereomers

(±)-α-(3-Benzoylphenyl) propionic acid (±)-**1**, is an analgesic and antiinflammatory agent, commercially known as ketoprofen[1]. In connection with a project on the synthesis of optically active antiinflammatory arylpropionic acid derivatives, we faced a clear and accurate determination of the absolute configuration of **1**. There were two reports by using circular dichroism technique[2].

Here, we would like to report that the absolute configuration of (±)-**1** was determined to be (*S*) by chemical correlation with (*S*)(+)-ethyl hydratropate (*S*)(+)-**10** by using Beckmann rearrangement.

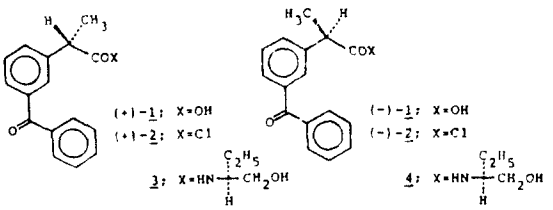


(±)-**1**



(S)(+)-**10**

As a resolving agent, (*S*)(+)-2-amino-1-butanol [α]+8.9°* was employed. The acid chloride **2**, which was obtained from **1** by treatment with oxalyl chloride in quantitative yield, was condensed with (*S*)(+)-2-amino-1-butanol by Schotten-Baumann method to afford diastereomeric amides **3** [α]-9.1° and **4** [α]-29.6°, which were separated by silica-gel column chromatography eluted with ether, in 27 and 28% yield, respectively. Hydrolysis of **3** and **4** yielded (+)-**1** [α]+48.8° and (−)-**1** [α]-47.7°** in 87 and 89% yield, respectively.

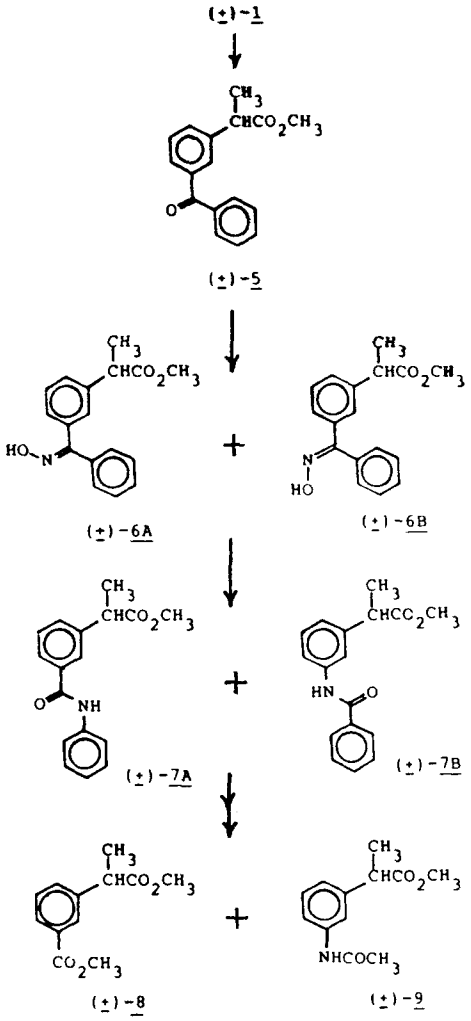


Since the absolute configuration of (+)-**10** is (*S*)[3], it was felt that the chemical correlation of (+)-**1** with (+)-**10** could be performed by using the Beckmann rearrangement as a key step. The possibility of the transformation was investigated by empolying (±)-**1** in place of (+)-**1** as shown in scheme I.

Treatment of **5**[4], obtained by esterification of **1**, with NH_2OH-HCl afforded geometrical diastereomers **6A** and **6B** in 90% yield. The NMR spectrum of the isomers showed two doublets, the peaks of the methyl group attached to an asymmetric carbon at δ 1.94(J=4.0 Hz) and δ 2.03 (J=4.0 Hz) and two singlets, those of the methyl group of ester at δ 4.10 and δ 4.20. The separation of the isomers could not be achieved by TLC. The Beckmann rearrangement of the oxime was effected to furnish amides in 92% yield. The amides were **7A** and **7B**, but they could not be isolated by TLC. Hydrolysis of amides followed by esterification and acetylation gave a mixture of acetanilide, **8**, methyl benzoate and **9** in 21, 17,

*Based on [α]+10.1° (neat) for pure (*S*)(+)-2-amino-1-butanol(Pitre, D. and Grabitz, E.B., Chimia, **23**, 399(1969).), the optical purity is 88%.

On the basis of [α]+57.1° (c=0.76, CH_2Cl_2) and [α]-57.7° (c=0.88, CH_2Cl_2) for pure (+)-1** and (−)-**1**(lit. 2a) and optical purity of (S)(+)-2-amino-1-butanol 88%, practically the optical purities correspond to 97 and 95%, respectively.



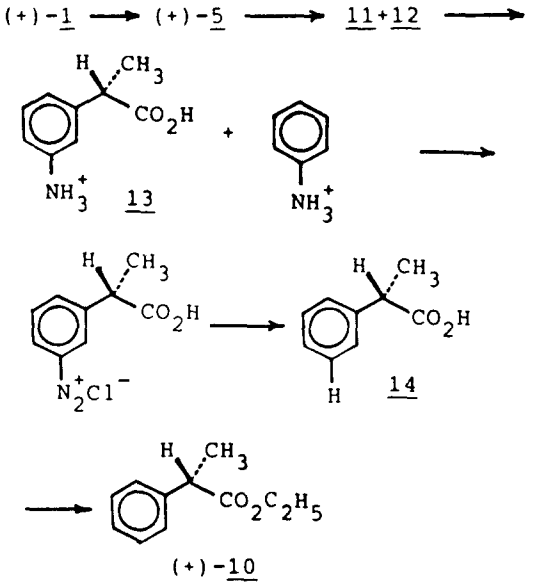
Scheme I

11 and 22% yield, respectively.

It was evident that **8** and acetanilide should result from **7A** while **9** and methyl benzoate from **7B**. The ratio of isolated yield of **8** and **9** was 10 to 13. It was equal to the ratio of the peak intensities corresponding to the afore-mentioned methyl group in the NMR of the mixture of **6A** and **6B**.

Consequently, this result indicated that **8** was from 6A through **7A** and **9** from **6B** through **7B** as shown in Scheme I. Since the transformation of **9** into **10** would easily be able to be achieved by hydrolysis, diazotization and reduction, we came to the conclusion that the Beckmann rearrangement could be applied to the elucidation of the absolute configuration of **1**.

The conversion of (+)-**1** into (+)-**10** was carried out by the same procedure as shown in scheme II.



Scheme II

The addition of NH_2OH-HCl to (+)-**5** [α]+69.6° , which was obtained by the esterification of (+)-**1** [α]+48.8° in 88% yield, was effected to afford oximes in 90% yield.

The oximes **11** and **12** corresponding to **6A** and **6B** were produced in the ratio of **10** to **13**, respectively. The Beckmann rearrangement of the oximes gave crude amides in quantitative yield. Hydrolysis of the amides and washing with ether gave the water fraction containing **13**, which was diazotized and treated with H_3PO_2.

Subsequently, the crude acid **14** was converted ethyl ester and purified by silica-gel column chromatography (ether: hexane=1 : 2) to (+)-**10** [α]+56.8° .

The positive rotation shows that there is an enantiomeric excess of the (*S*)-**10**. Therefore the absolute configuration of (+)-**1** was determined to be (*S*).

EXPERIMENTAL METHODS

All melting points were determined on a Buchi model 510 apparatus and are uncorrected. Optical rotations were measured on a Jasco model DIP-181 polarimeter. IR spectra were obtained with a Beckmann model IR-20A spectrometer and NMR spec-

tra were taken on a Varian model 360A (60 MHz) spectrometer with TMS as internal standard. Mass spectra were obtained with Hewlett Packard model 5985B GC/MS spectrometer.

***Preparation of* (+)-1 *and* (−)-1**

(*S*)(+)-2-Amino-1-butanol [α]+8.9° (10.8g, 120 mmole) was dissolved in dry acetone (50 *ml*) cooled in an ice bath and an acetone soln of **2** (22 g, 80 mmole), which was obtained from **1** ($(COCl)_2$, 60℃, 2 hrs; y. quant.), and the 2N -NaOH soln (41 *ml*, 80 mmole) were simultaneously added over 1 hr. Then the reaction mixture was stirred for 2 hrs and submitted to evaporation *in vacuo* to remove acetone. The mixture was extracted with AcOEt and the organic layer was washed with brine and dried with $MgSO_4$. Evaporation of the solvent gave crude **3** and **4** as viscous oil. After silica-gel column chromatography (ether only), the faster diastereomer **3** was a viscous, non-crystallizable substance (6.85g, 27%) and the slow one **4** a white solid (7.2g, 28%). **3**; caramel, [α]-9.1° (c=0.99, MeOH), IR(neat) cm^{-1}, 3400~3200(OH), 3300(OH), 1655(amide), NMR($CDCl_3$) δ 8.35~7.8(9H, m, aromatic H), 7.0(1H, d, J=8 Hz, NH), 4.5~3.9(5H, m, OH, CH×2, CH_2O), 2.2~1.6(2H, m, CH_2), 2.0(3H, d, J=7 Hz, CH_3), 1.37(3H, t, J=7 Hz, CH_3), MS, m/z 325(M^+), 295, 254, 237, 210, 105, 77, 58. **4**; mp 70-72℃, [α]-29.6° (c=0.66, MeOH), IR(nujol) cm^{-1}, 3400~3200 (OH), 3300 (OH), 1660(amide), NMR($CDCl_3$) δ 8.35~7.8(9 H, m, aromatic H), 7.0(1H, d, J=8 Hz, NH), 4.5 ~3.9 (5H, m, OH, CH×2, CH_2O), 2.1~1.55(2H, m, CH_2), 1.96(3H, d, J=7 Hz, CH_3), 1.23(3H, t, J=7 Hz, CH_3), MS, m/z 325(M^+), 295, 254, 237, 210, 105, 77, 58.

The hydrolysis of **3** (6.8g, 20 mmole) in 20% HCl at 60℃ for 2 hrs gave (+)-**1** as a white solid (4.42g, 87%), mp 69~69.5℃, [α]+48.8° (c=0.76, CH_2Cl_2).

The same treatment of **4** (7.2g, 22.8 mmole) gave (−)-**1** as a white solid (5g, 89%), mp 69~70℃, [α]-47.7° (c=0.88, CH_2Cl_2).

***Preparation of* (±)-5**

The esterification of (±)-**1** (4g, 15.7 mmole) in methanol with a few drops of c-H_2SO_4 for 4 hrs gave (±)-**5** as pale yellow, viscous oil (3.7g, 90%), IR(neat) cm^{-1}, 1735(ester), 1655(ketone), NMR(CCl_4), δ 7.85~7.2(9H, m, aromatic H), 3.7(1H, q, J=7 Hz, CH), 3.63(3H, s, OCH_3), 1.48(3H, d, J=7 Hz, CH_3), MS, m/z 268(M^+), 236, 209, 191, 181, 165, 131, 105, 77, 59.

Preparation of* 6 4+6*B

To a methanol soln of (±)-**5** (36.1g, 13.5 mmole), dry pyridine (10 m*l*) and NH_2OH-HCl (1.2 g, 17.3 mmole) were successively added and the mixture was refluxed for 3 hrs.

After evaporation of methanol, the residue was diluted with ether and the ether layer was washed with 5% HCl, water and brine. Drying($MgSO_4$) and evaporation gave **6**, as pale yellow, viscous oil (3.5g, 90%), IR(neat) cm^{-1}, 3400(OH), 1740 (ester), NMR($CDCl_3$, external TMS) δ 8.0~7.8(9 H, m, aromatic H), 4.4~4.1(1H, m, CH), 4.2(1.7 H, d, J=4 Hz, CH_3), 1.94(1.3H, d, J=4 Hz, CH_3).

Preparation of* 7*A*+7*B

To a dry thiophene-free benzene soln of **6** (3.3g, 11.7 mmole), was added PCl_5 (4g, 19.2 mmole) powder and the mixture was stirred for 2.5 hrs. After dist. H_2O was added slowly, the mixture was diluted with benzene.

The benzene layer was washed with brine and dried with $MgSO_4$. Evaporation of the solvent gave the mixture of amides **7A** and **7B** as viscous oil (7g, 92%), IR(neat) cm^{-1}, 3280(NH), 1730 (ester), 1650(amide), NMR($CDCl_3$, external TMS) δ 9.3(1H, s, NH), 8.4~7.4(9H, m, aromatic H), 4.3~4.05(1H, m, CH), 4.08(3H, s, OCH_3), 1.9 (3 H, d, J=7 Hz, CH_3).

***Preparation of* 8 *and* 9**

The 20% HCl soln of amides **7A** and **7B** (3g, 10.6 mmole) was stirred for 15 hrs at 60℃ and then extracted with ether. The ether fraction was dried with $MgSO_4$ and evaporated to afford to the white solid.

The esterification of the solid with diazomethane and column chromatography (ether: hexane=1 : 5) gave **8**: IR(neat) cm^{-1}, 1740(ester), 1710(ester), NMR(CCl_4) δ 7.9~7.4(4H, m, aromatic H), 3.9~3.5(1H, m, CH), 3.88(3H, s, OCH_3), 3.63(3 H, s, OCH_3), 1.48(3H, d, J=8 Hz, CH_3), MS, m/z 222(M^+), 191, 163, 131, 103, 91, 77, 59 and methyl benzoate.

The water fraction was acetylated with acetic anhydride, and then esterification with diazomethane and column chromatography (ether: hexane= 4 : 1) of the resulting pale-yellow oil gave **9**: IR(neat) cm^{-1}, 3260(NH), 1750(ester), 1660(amide), NMR(CCl_4) δ 9.4(1H, s, NH), 7.7~6.8(4H, m, aromatic H), 3.7~3.4(1H, m, CH), 3.53(3H, s, OCH_3), 2.1(3H, s, CH_3), 1.35(3H, d, J=8 Hz, CH_3), MS, m/z 221(M^+) 179, 162, 120, 91, 77, 65, 43 and acetanilide.

***Preparation of* (+)-5**

The same treatment of (+)-**1** as before -mentioned esterification afford to (+)-**5** [α]+69.6° (c=1.29, MeOH), which was identified with (±)-**5** by all physical and spectroscopic data.

***Preparation on* 11+12**

The same treatment of (+)-**5** as above -mentioned preparation of oxime and Beckmann

rearrangement afford to **11**±**12**, which were identified with **7A**+**7B** by all physical and spectroscopic data.

Preparation of (+)-**10**

The 20% HCl soln of amides **11**+**12**(3g, 10.6 mmole) was stirred for 15 hrs at 60℃ and washed with ether. To water fraction containing HCl salt of 2-aminohydratropic acid and aniline, c-HCl(5 *ml*) and an aqueous $NaNO_2$(1g, 14.5 mmole) were successively added in an ice bath and the mixture was stirred for 1 hrs.

Then an aqueous 30% H_3PO_2(20 *ml*, 11.7 mmole) was added for 15 mins and the mixture was stirred for 24 hrs at 0℃. After addition of ether to the resulting soln, the ether layer was separated and washed with brine and dried with $MgSO_4$. Evaporation of ether gave **14** as a red oil (745 mg, 78%).

The esterification of which was refluxed with a few drops of c-H_2SO_4 in ethanol for 24 hrs, which was followed by column chromatography(ether: hexane=1 : 2) afforded to the pure **10** as a pale yellow oil(400 mg, 45%), $[\alpha]+56.8°$ (c=2.10, EtOH), IR(neat) cm^{-1}, 1740(ester), NMR($CDCl_3$) δ 7.33(5H, s, aromatic H), 4.15(2H, q, J=7 Hz, OCH_2), 3.6(1H, q, J=7 Hz, CH), 1.5(3H, d, J=7 Hz, CH_3).

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