DAEHAN HWAHAK HWOEJEE
(*Journal of the Korean Chemical Society*)
Vol. 22, No. 1, 1979
Printed in Republic of Korea

# 사염화탄소와 트리페닐포스핀을 사용한 스테로이드 링 A 옥심의 벡크만 자리옮김반응

金正均 · 崔舜圭 · 朴恒雨 · 李庸泰*

부산대학교 문리과대학 화학과
*영남대학교 문리과대학 화학과

(1978. 11. 1 접수)

# Beckmann Rearrangement of Ring A Steroidal Oxime Using the Carbon tetrachloride-triphenylphosphine

**Jack C. Kim, Soon-kyu Choi, Won-Woo Park** and **Yong-Tae Lee***

*Department of Chemistry, Busan National University, Busan 607, Korea*

**Department of Chemistry, Youngnam University, Kyungsan 632, Korea*

(Received Nov. 1, 1978)

**요 약.** 벡크만 자리옮김반응의 실험조건은 대부분이 센산 (HCl, $H_2SO_4$, $PCl_5$ 등)이나, 고온과 같은 격렬한 반응조건을 사용하므로 이러한 조건은 자주 전위보다는 케토옥심의 이성질화를 일으킨다. 5α-cholestan-3-one oxime의 벡크만 전위에 온화하고 중성의 조건인 사염화탄소와 트리페닐포스핀을 사용하여 3-aza-A-homo-5α-cholestan-4-one을 얻었다.

이러한 새롭고, 온화하며 쉽고 빠른 벡크만 전위를 소개하고 이러한 방법을 고전적인 벡크만 전위 시약인 폴리인산을 사용한 방법과 비교하였다.

**ABSTRACT.** The experimental procedures of Beckmann rearrangement mostly involve the use of vigorous conditions such as strongly acidic reagents (conc. HCl, $H_2SO_4$, $PCl_5$, *etc.*) or elevated temperatures, which frequently cause isomerization of ketooximes prior to rearrangement. We have effected the Beckmann rearrangement on 5α-cholestan-3-one oxime using the carbon tetrachloride-triphenylphosphine reagent under mild, neutral conditions to give 3-aza-A-homo-5α-cholestan-4-one. This new, mild, facile and rapid general method of Beckmann rearrangement is presented, and compared with the classical (more conventional) Beckmann reagent of polyphosphoric acid.

## INTRODUCTION

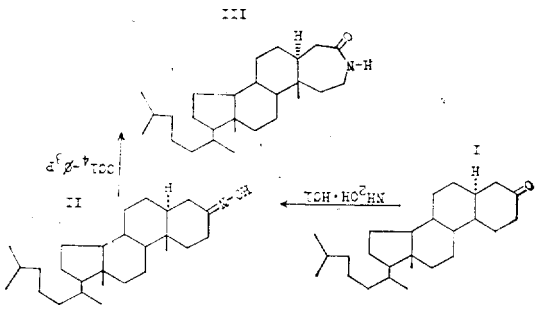
The interesting pharmacological properties of steroid alkaloids in modern medicine and the great value of the steroids have brought about an increasing interest in amino-steroids. Beck-

mann and Schmidt rearrangements offered two convenient methods for introducing a hetero-nitrogen into the steroid ring system. The transformations of ketooximes to amides (or lactams) have been prepared by the Beckmann rearrangement using a variety of solvents, and such catalysts as phosphorous oxychloride,[1] formic acid[2], *p*-acetamidobenzene sulfonyl chloride[3], sulfuric acid[4], thionyl chloride[5], and others[6]. The Schmidt rearrangement has been applied to a few ketooximes with sulfuric acid being used as the catalyst in the presence of a suitable organic solvent.

The low yields obtained by these conventional methods have been variable. Even though the Beckmann rearrangement of ketooximes to amides has widespread synthetic applications[7], the conventional procedures generally require the vigorous conditions such as strongly acidic reagents[8] or elevated temperatures, causing isomerization of the oximes prior to rearrangement.

We now wish to report a facile and rapid general method of Beckmann rearrangement of immediate utility for the synthesis of lactam. The literature survey has shown that the carbon tetrachloride-triphenylphosphine reagnet[10] will effect the Beckmann rearrangement on a variety of alkanone oximes. The rearrangement proceeds under mild, neutral conditions to give lactams in yields of 50~70 %.

In order to obtain a preliminary evaluation of the usefulness of $CCl_4$-$Ph_3P$ reagent for the introduction of a hetero-nitrogen atom into the steroid ring system (called aza-steroid), 3-aza-A-homo-5$\alpha$-cholestan-4-one (III) was synthesized by the Beckmann rearrangement using both a new reagent $CCl_4$-$Ph_3P$ reagent, and more conventional method (used by polyphosphoric acid). Shoppee and Sly[11] prepared this aza-steroid, 3-aza-A-homo-5$\alpha$-cholestan-4-one



by the Beckmann rearrangement of 5$\alpha$-cholestane-3-one oxime (II), using thionyl chloride as the catalyst and dioxane as the solvent. The crude yields reported[11] were not satisfactory.

## EXPERIMENTAL

**General.** Reagnets grade chemicals were purified by recrystallization or by distillation just before use; tetrahydrofuran was dried over excess lithium aluminium hydride and distilled before use. Melting points were uncorrected, and Perkin-Elmer 267 Grating IR Spectrophotometer was used. Homemade TLC plates were made by mixing silica gel G (Merck) 35 g with $CHCl_3$: $CH_3OH$ (2 : 1, v/v) 100 m*l*, and elution solvents were A;$C_6H_6$: EtOAc : $CH_3OH$ (85:5:10), and B;$CHCl_3$ : $CH_3OH$ : EtOAc (2:1:1).

**Syntheses. 5$\alpha$-Cholestane-3-one Oxime (II).** To a solution of 0.5 g (1.29 mmole) of 5$\alpha$-cholestan-3-one in 30 m*l* of methanol and 5 m*l* of water were added 0.2 g of potassium carbonate and 0.36 g (5.17 mmole) of hydroxyl amine hydrochloride, and the mixture was refluxed on a steam bath for one hour. Excess cold water was added to the reaction mixture; the solid which separated was collected after thorough chilling, and was recrystallized from methanol to afford 0.49 g (94 %) of a white solid, m. p 200~201°C (*lit.*[12] m. p 100~201°C). The ir (KBr) lacked a sharp band at 1700 $cm^{-1}$ and appeared absorption bands at 1630 $cm^{-1}$

(-C=N)oxime) and 3400 $cm^{-1}$ (-C-H oxime).

**3-Aza-A-homo-5α-cholestan-4-one (III). Using the Carbon tetrachloride-triphenylphosphine Reagent.** Toaa round bottom flask equipped with a reflux condenser (drying tube), magnetic stirrer and heating mantle, was introduced a mixture of 0.5g (1.2 mmole) of II, 0.63 g (2.4 mmole) of triphenylphosphine and 12 m*l* of carbon tetrachloride. The reaction mixture was stirred and brought to a reflux for 4.9 hours. Semi-solids appeared in 1.5 hours and stirring was continued to prevent bumping. After cooling and filtering, the semi-solids were crystallized from ethyl alcohol (charcoal) to obtain 0.38 g (78 %) of a white solid, m.p 275~277°C (*lit.*[11] m.p 275.5~276.5°C). Mixed melting point determination obtained by the PPA method, gave no depression. The ir (KBr) showed appearances of bands at amide band I (1650 $cm^{-1}$) and amide II (3440 $cm^{-1}$). The *Rf* values are 0.31 and 0.86 on respective solvents A, and B.

**3-Aza-A-homo-5α-cholestan-4-one (III). Using the Polyphosphoric Acid. Polyphosphoric Acid Preparation.** Polyphosphoric acid was made before use; To an ice-cold 100 m*l* of phosphoric acid was added slowly 200g of $P_2O_5$ and the mixture was mannually stirred for 7 hours at the oil bath temperature of 130°C. A mixture of 15m*l* of PPA and 0.5 g (1.2 mmole) of II was heated, with manual stirring, to 130 °C (oil bath) and maintained at this temperature for 0.5 hours. Then the mixture was poured into 100 g of crushed ice, and left the whole mixture in the refrigerator overnight, and neutralized with sodium bicarbonate, and extracted with chloroform (3×50 m*l*). Removal of the solvent, after drying over anhydrous sulfate, gave a solid residue. This residue was crystallized from methanol to give 0.28 g (57.5 %) of a white solid, m.p is identical to that of the authentic sample. The mixed *Rf* observation with this sample and that obtained by $CCl_4$-$Ph_3$ reagent was identical.

## RESULTS

In this preliminary experiment, it has been demonstrated that the 3-aza-A-homo-5α-cholestan-4-one (III) was readily prepared from 5α-cholestan-3-one (II) in high yield by the new reagent, triphenylphosphine-carbon tetrachloride. No solvent was needed since $CCl_4$ is a good solvent for 5α-cholestan-3-one oxime(II). The condition we used, was the reflux temperature of $CCl_4$, and no special handling precautions appeared to be neccesary, although the rearrangements were run under reasonably anhydrous conditions of $CCl_4$.[13] The reaction time was only 4 hours. The yield of analytically pure product was at least 78 %.

The aza-steroid, 3-aza-A-homo-5α-cholestan-4-one (III) obtained by the conventional method of Beckmann rearangement using polyphosphoric acid (See Experimental) as a catalyst, gave troublesome, erratic lower yields than the above new method. The vigorous heating tempeature of 130°C for 7 hours by the conventional PPA Beckmann method was comparable with the mild temperature of 76°C for 2 to 4 hours. These mild, neutral condition given by the new reagent, $CCl_4$-$Ph_3P$ for the synthesis of the aza-steroid in the Beckmann rearrangement, would offer even greater advantages of many steroids which contain functional groups sensitive to vigorous conditions such as strongly acidic reagents or elevated temperature.

To the best of our knowledge, this $CCl_4$-$Ph_3P$ procedure in the Beckmann rearrangement is the first demonstration in this aza-steroid synthsis series. Mechanistic details were not investigated[14]. The fact that the lactam (III) apparently formed directly and the expected imidoyl

chloride was not observed first, indicated the probable presence of water despite our precautious anhydrous condition used. Mechanistic opinions of this reagent will be discussed in a future communication.

## REFERENCES


1. Beckmann, *Ber.*, **19**, 988 (1886).
2. T. Vanes, *J. Chem. Soc.*, 3883 (1965).
3. S. T. Kaufmann, *J. Amer. Chem. Soc.*, **73**, 1979 (1951).
4. H. Stehpen and B. Stasum, *J. Chem. Soc.*, 980 (1656).
5. N. J. Doorenbos and M. T. Wu, *J. Org. Chem.*, **26**, 2548 (1961).
6. S. Hara, *Yakugaku Zasshi*, **78**, 1030 (1958).
7. L. G. Donaruma and W. G. Heldt, "The Beckmann Rearrangement", Vol. 11, P. 1~56, Organic Reactions, John Wiley and Sons, New york, 1960.
8. I. Fleming and R. B. Woodward, *J. Chem. Soc.*, **1**, 1653 (1973).
9. M. Hono and I. Sakai, *Tetrhedron Letters*, 4541 (1965).
10. I. M. Downie and J. B. Holmes, J. B. Lee, *Chem. and Ind.*, 900 (1966).
11. C. W. Shappee and J. C. Sly, *J. Chem. Soc.*, 3458 (1958).
12. R. C. Craig, *J. Amer. Chem. Soc.*, 84, 3410 (1962).
13. H. Szmant, *J. Org. Chem.*, **30**, 1338 (1965).
14. E. Yamato and S. Sugasawa, *Tetrahedron Letteres*, 4383 (1970).