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단 신

트리페닐포스핀과 사염화탄소를 사용하여 Cholest-4-ene-3-one Oxime으로부터 3-Aza-A-homo-cholest-4-one-4a-ene의 合成

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Preparation of 3-Aza-A-homo-cholest-4-one-4a-ene from the Cholest-4-ene-3-one Oxime Using the Triphenylphosphine-Carbon Tetrachloride Combinations

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Azasteroids, a steroid possessing nitrogen atom in nucleus, have been in vestigated for a wide variety of medicinal interests, such as coronary dilatory[1], hypotensive[2], antimicrobial[3], an others.[4] There are few reports on the preparation of synthetic azasteroids. For example, Beckann and Schmidt rearrangements offered two convenient methods for introducing a hetero-nitrogen atom into the steroid ring systems.

The yields of the steroid lactams obtained by Beckmann and Schmidt rearrangements of steroid ketooximes have been reported to be low and variable, even thogh the rearrangements have wide-spread synthetic applications[5]. The classical conventional procedures generally require the vigorous conditions such as strongly acidic reagents or elevated temperatures, causing isomerization of the ketooximes prior to the desired rearrangement[6], and are not universally applicable.[7]

EXPERIMENTAL

Melting points were determined with Polytemp(Polyscience Corporation) and Fisher-Johns apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-360 spectrometer in chloroform-*d* with TMS as an internal standard, uv spectra with a Hitachi-124 in ethanol, and ir spectra with Shimadzu 400 spectrophotometer. The tlc plates were made by mixing Silica Gel G Type 60 (Merck) 35g with chloroform: methanol (2 : 1, v/v) 100m*l*, and their chromatograms were developed with A; benzene: ethyl acete (80 : 20, v/v) and B; benzene: ethyl acetate:methanol (85 : 5 : 10, v/v) and detected by iodine vapor.

3-Aza-A-homo-cholest-4-one-4a-ene.

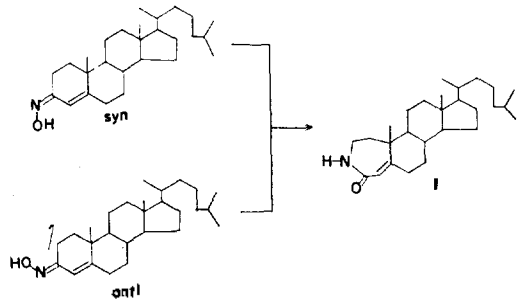
Reaction in Carbon Tetrachloride. To a well-dried, round, round-bottom flask equipped

with a reflux condenser (drying tube), magnetic stirrer and heating mantle, were placed 1.00 g (2.5 mmole) of cholest-4-ene-3-one oxime[9] (double m.p 66 °C and 154~156 °C), 1.26g (2.5 mmole) of triphenylphosphine and 50 ml of anhydrous carbon tetrachloride. The reaction mixture was refluxed with stirring for 5 hours. The flask was then cooled to room temperature and 30 ml of *n*-pentane was added to, precipitate the bulk of the triphenylphosphine oxide. The oxide was filtered off and the filtrate was evaporated in vaccuo affording the light yellow *semi*-solid. Crystallization from ethanol (charcoal treatment) gave 0.82 g (82 %) of a white solid, m.p 251~254 °C (*lit.*[10] m.p 250~254 °C). The purity was established by tlc and the R_f values were 0.57 and 0.41 on the respective solvents A and B. λ_{max}^{EtOH} 223nm (log 4.1). Ir (KBr), 3258, 3150, 3070 (-NH-), 1656, 1628 (-NHCO-), 1612 (C=C-C=O), 997 cm^{-1}. nmr ($CDCl_3$), 1.10 (*s*, 19-CH_3), 3.23 (*m*, -CH_2-N-), 6.30 (*s*, 4a-H).

Beckmann Rearrangement Using PPA. Polyphosphoric acid was was made before use. To an ice-cold 100 ml of phosphoric acid was added slowly 200 g of phosphorous penaoxide and the mixture was mannually stirred for 7 hours at the oil bath temperature of 130 °C. A mixture of 30 ml of PPA and 1.00 g (2.5 mmole) of cholest-4-ene oxime[9] was heated with manual stirring to 130 °C (oil bath) and maintained at this temperature for 1 hour. Then the mixture was poured into 100 ml of crushed ice-water and left the whole mixture in the refrigerator overnight, and neutralized with sodium bicarbonate and extracted with chloroform (3×50 ml) and dried (magnesium sulfate). Filtration and concentration gave a *semi*-solid which was crystallized from ethanol (charcoal treatment) to afford 0.42 g (42 %) of white solid. Melting point was identical with this sample and that of authentic sample. The mixed R_f observation with this sample and that obtained by the triphenylphosphine-carbon tetrachloride reagent was identical.

RESULTS AND DISCUSSION

The starting material, cholest-4-ene-3-one oxime[9] obtained from the cholest-4-ene-3-one gave double melting point at 66 °C and 154~156 °C, probably due to the presence of geometric isomers of *anti*- and *syn*-cholest-4-ene-3-one oximes. The attempt to separate geometric isomers by fractional crystallization was not successful and the tlc elution on solvents A and B showed identical R_f values.



In this preliminary experiment, we reacted directly the geometric mixtures of isomeric *anti*- and *syn*-cholest-4-ene-3-one oximes with the triphenylphosphine-carbon tetrachloride combination, and obtained 84 % yields of a desired transformation product, 3-aza-A-homocholest-4-one-4a-ene[10] which is identical with that of the compound prepared by the classical Beckmann rearrangement of cholest-4-ene-3-oneoxime (See Experimental), in view of the spectral characterization of the nmr, uv, and ir spectra and the result of the mixed melting point determinations, along with the R_f values on the tlc chromatograms.

The 3-aza-A-homo-cholest-4-one-4a-ene obtained by the conventional method of Beckmann

rearrangement using polyphosphoric acid gave troublesome, erratic results of lower yields (42 %). The vigorous heating temperature of 130 °C for 7 hours was comparable with the triphenylphosphine-carbon tetrachloride method which is characterized by the extremely mild, neutral condition and easy work-up procedures of the reaction product (See Experimental). This facile and rapid, mild reagent of triphenylphosphine-carbon tetrachloride combination would offer even greater advantages of many steroids which contain functional grous sensitive to vigrous conditions such as strongly acid ic reagents or elevated temperatures.

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