

UNITED STATES PATENT OFFICE

2,531,441

REARRANGEMENT OF STEROID OXIMES

Percy L. Julian, Maywood, and John W. Cole and Edwin W. Meyer, Chicago, and Arthur Magnani, Wilmette, Ill., assignors to The Glidden Company, Cleveland, Ohio, a corporation of Ohio

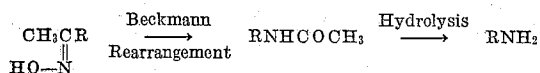
No Drawing. Application May 22, 1947,
Serial No. 749,888

20 Claims. (Cl. 260—397.5)

1

The present invention relates to the production of steroid amines from steroid methyl ketones.

For many years one of the best procedures for shortening a carbon-carbon chain has been the Beckmann rearrangement of ketonic oximes. This is illustrated by the following equation:



Such a degradation thus shortens the chain by two carbon atoms. A procedure of this type would be very valuable in the steroid series where a major problem is to degrade the side-chain by simplified procedures. Many known procedures frequently involve numerous individual operations which are tedious and many of which result in ultimate low yields.

As will be seen from the equation above, the Beckmann rearrangement of the oxime of a methyl ketone leads always to the acetyl derivative of the desired amine, i. e. to an amide. To secure the desired amine this amide must be subjected to hydrolysis as is also indicated in the equation above. In the case of amides where R represents a sterically hindering group, hydrolysis is exceedingly difficult and sometimes impossible. This is illustrated by the classic example of acetyl-mesidine which can be hydrolyzed only with great difficulty. Steroid amides where R represents a cyclopentanopolycyclophenanthrene nucleus are even more difficult to hydrolyze than acetyl-mesidine. The steroid nucleus occupies considerable space and groupings attached to certain atoms of said nucleus are spatially hindered to a very great extent.

Thus the Beckmann rearrangement of the oxime of the important methyl ketone, Δ^5 -pregnene-3-ol-20-one, would provide a most useful method for the preparation of intermediates for valuable therapeutic compounds, were it not for the fact that the resulting acetyl-17-amine hydrolyzes with extreme difficulty. U. S. Patent 2,212,363 describes the Beckmann rearrangement of the oxime of this pregnenolone, but the commercial exploitation of the idea is nullified by the impracticability of the hydrolysis of the resulting acetyl-amine.

It is accordingly an object of the present invention to provide an improved process for the degradation of the side-chain of steroids.

A further object is to provide a simplified process

2

for the degradation of the side-chain of steroids.

Another object is to provide an improved process for producing amines of the steroid series.

A specific object is to provide an improved process for producing steroid amines from the oximes of steroid methyl ketones.

A further specific object is to provide a process for producing steroid amines from the oximes of steroid methyl ketones without passing through the intermediate difficultly hydrolyzable acetyl derivatives of the amines.

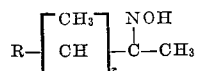
Other objects will be apparent to those skilled in the art from the following description.

In the classical Beckmann rearrangement of the oximes of methyl ketones, the end result is that the original acetyl group of the methyl ketones has lost its bond to carbon and is attached only to nitrogen. Since most organic rearrangements of this type are postulated to proceed through unstable intermediates, it would be desirable to carry out the rearrangement reaction in a medium which would fix the acetyl group in the form of a stable compound other than the steroid amide, and thereby promote the formation of the free steroid amine derived from the original oxime. In the light of modern concepts the essential constituent of such a medium would be considered as a favored "acceptor" for the acetyl group, in much the same manner as certain ketones act as acceptors for hydrogen in oxidation reactions.

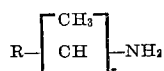
It has been found that the above can be realized in practice by treatment of the sulphonic acid esters of oximes of steroid methyl ketones in a medium, the essential constituent of which is a compound of the general formula HR' , where R' is a negative organic radical which combines readily with an acetyl group to form compounds wherein the R' group is replaceable by an OH group on hydrolysis. Thus on dissolving the sulphonic acid ester of the oxime in an alcohol, a primary or secondary amine, an alcohol amine, or a diamine, rearrangement of the oxime derivative takes place in such manner as to produce as the end product the free amine rather than the acetyl derivative of said amine. As a general rule the reaction is accelerated by warming. It is not necessary that the acetyl acceptor be the solvent in the reaction, so long as it is present in the reaction medium in sufficient quantities to bind the acetyl group. As a rule it is desirable that it be present in generous excess.

3

The oximes which lend themselves to the above described treatment may be characterized by the general formula



wherein R stands for a saturated or unsaturated cyclopentanopolyhydrophenanthrene nucleus and x is zero or 1. The desired amines are represented by the general formula



where x is again zero or 1.

That the process of this invention is a novel rearrangement of oximes is attested by the fact that, first, the end products are free amines rather than acetyl amines, and second, that treatment of the acetyl amines, secured by a normal Beckmann rearrangement, with the reagents described above, does not result in hydrolysis to the free amines.

The following examples are illustrative of the invention.

Example I

A solution of 5.0 g. of Δ^5 -pregnene-3-ol-20-one acetate oxime in 15 cc. of pyridine was chilled in an ice bath and then treated with 5.0 g. of p-toluenesulfonyl chloride with shaking. The temperature of the reaction was kept below 60° F. until no further heat developed. After standing for four hours at room temperature, the reaction mixture was treated with 30 cc. of ethanolamine and heated on a steam bath for two hours. 30 cc. of methanol and 10 cc. 25% sodium hydroxide solution were added and the mixture was steam distilled until all the pyridine was removed and the product crystallized. The crude 3-hydroxy-5-androstene-17-amine was filtered, washed with water and dried, M. P. 155-160° C. The yield of amine was 87% of the theoretical.

Example II

A cold solution of 3.74 g. of pregnenolone acetate oxime in 15 cc. of pyridine was treated with 3.74 g. of p-toluenesulfonyl chloride and allowed to stand in the ice-box for twelve hours. It was then poured over ice and 10 cc. of concd. sulfuric acid and extracted with benzene-ether. The extract was washed with water, dried and concentrated in partial vacuum. The product was crystallized from benzene-petroleum ether (B. P. 35-60° C.). There resulted 4.7 g. of pregnenolone acetate oximino-p-toluenesulfonate melting at 126.5-130° C. with decomposition.

The p-toluenesulfonate was suspended in 20 cc. of ethanolamine and heated on a steam bath for two hours. The solution was then worked up as described in Example I. For purpose of identification the 3-hydroxy-5-androstene-17-amine was converted to the benzal derivative which melted at 241-243° C. The yield of the amine amounted to 92.5% of theory.

Example III

A cold solution of 5.0 g. of pregnenolone acetate oxime in 15 cc. of pyridine was treated with 5.0 g. of benzenesulfonyl chloride as described in Example I. The work-up followed the procedure of that example. The isolated 3-hydroxy-5-androstene-17-amine gave the same benzal compound as described in Example II.

4

Example IV

The pregnenolone acetate oximino-p-toluenesulfonate was prepared as described in Example II. A suspension of 4.7 g. of the sulfonate ester in 20 cc. of cyclohexylamine was heated on a steam bath with swirling. The solid dissolved rapidly. The solution was then heated for two hours. After the addition of 10 cc. of 10% sodium hydroxide solution, the mixture was steam distilled. As distillation took place the product slowly separated in crystalline form. The crude 3-hydroxy-5-androstene-17-amine was separated by filtration, washed with water and dried.

The amine was converted to the benzal derivative for characterization.

Example V

A solution of 3.2 g. of p-toluenesulfonate of Example II in 10 cc. of methanol and 10 cc. of cyclohexylamine was refluxed for two and one-half hours. The solution was diluted with methanol and 10 cc. of 10% sodium hydroxide solution and steam distilled. As the alcohol and cyclohexylamine separated, the product crystallized. The crude 3-hydroxy-5-androstene-17-amine was separated by filtration, washed with water and dissolved in 40 cc. of methanol. The amine was converted directly to the benzal derivative by treatment of the methanolic solution with 1 cc. of benzaldehyde. The separated crystalline benzal compound was then decomposed by refluxing with 5 cc. of 10% hydrochloric acid in methanol followed by steam distillation to remove benzaldehyde. There remained the hydrochloride of 3-hydroxy-5-androstene-17-amine. The free amine was recovered by decomposing the hydrochloride with alkali, extracting with ether and concentrating the ether solution.

Example VI

A solution of 2.64 g. of the p-toluenesulfonic ester of Example II in 50 cc. of ethanol saturated with ammonia was refluxed for two hours. After dilution with methanol, the solution was steam distilled. The separated product was dissolved in methanol, treated with 1 cc. of benzaldehyde and several cc. of 10% sodium hydroxide solution. The crystalline benzal compound which formed was converted to 3-hydroxy-5-androstene-17-amine as described in Example V.

Example VII

A solution of 2.64 g. of pregnenolone-acetate oximino-p-toluenesulfonate in 20 cc. of aniline was heated on the steam bath for two hours. It was then diluted with 75 cc. of methanol, made alkaline with a few cc. of 10% sodium hydroxide solution and steam distilled to remove methanol and aniline. The crude amine was separated by filtration. For purification it was dissolved in 250 cc. of methanol containing 3 g. of potassium hydroxide. After refluxing for one hour, the major portion of the alkali was neutralized with glacial acetic acid. The benzal derivative of the amine separated upon treatment of the methanolic solution with 2 cc. of benzaldehyde. The benzal compound was converted to the 3-hydroxy-5-androstene-17-amine by the hydrolysis described in Example V.

Example VIII

2.64 g. of pregnenolone acetate oximino-p-toluenesulfonate was treated with 20 cc. of ethylcyclohexylamine in the same manner as described

5

in Example VII. The crude 3-hydroxy-5-androstene-17-amine was characterized as the benzal derivative.

Example IX

A solution of 2.64 g. of pregnenolone acetate oximino-p-toluenesulfonate in 10 cc. of dry benzene and 10 cc. of n-butylamine was refluxed for two and one-half hours, diluted with methanol and steam distilled. The crude amine, 3-acetoxy-5-androstene-17-amine, which separated was characterized as the benzal derivative, M. P. 195-198° C. The yield was 77% of theory.

Example X

2.64 g. of pregnenolone acetate oximino-p-toluenesulfonate was dissolved in 20 cc. of ethylenediamine and heated on a steam bath for two hours. The solution was diluted with methanol and steam distilled. The crystalline product was separated by filtration, washed with water and dried. The practically pure 3-hydroxy-5-androstene-17-amine melted at 163-168° C. The yield was 96% of the theoretical yield.

Example XI

3.76 g. of 3-acetoxy-allo-pregnane-20-one oxime was dissolved in 15 cc. of pyridine and treated with 3.76 g. of p-toluenesulfonyl chloride with cooling. After standing at room temperature for four hours, the solution was diluted with 30 cc. of ethanolamine and heated on a steam bath for two hours. It was then diluted with methanol and steam distilled. The crude amine, 3-hydroxy-androstane-17-amine, was separated by filtration, washed with water and dried. For characterization the amine was converted to a benzal derivative which melted at 208-212° C.

Example XII

4.0 g. of the oxime of 3-acetoxy-5-tenor-cholenyl methyl ketone was dissolved in 12 cc. of pyridine and treated with 6.0 g. of toluenesulfonyl chloride with chilling. After standing at room temperature for four hours, the mixture was diluted with 30 cc. of ethanolamine and heated on a steam bath for two hours. The resulting solution was diluted with methanol, made alkaline with 10 cc. 10% sodium hydroxide and steam distilled to remove methanol and pyridine. The crude 3-hydroxy-5-pregnene-20-amine was separated. After crystallization from hexane-methanol it melted at 173-174° C. The amine can be converted to a benzal derivative which melts at 187-188° C.

Example XIII

A solution of 3.7 g. of pregnenolone acetate oxime in 15 cc. of pyridine was treated with 3.75 g. of p-toluenesulfonylchloride with cooling and then allowed to stand at room temperature for four hours. The excess pyridine was removed in good vacuum with gentle warming. The solid which remained was dissolved in 30 cc. of ethanol and the solution was refluxed for two hours. A solution of 5.0 g. of potassium hydroxide in 40 cc. of 75% aqueous ethanol was added and refluxing continued for another hour. The solution was steam distilled and the crude 3-hydroxy-5-androstene-17-amine separated by filtration.

The above procedure may be carried out without removal of the excess pyridine.

Example XIV

Pregnenolone acetate oximino-p-toluenesulfonate was prepared as described in Example II.

6

A solution of 4.8 g. of the ester in 30 cc. of ethanol was refluxed for three hours, made alkaline with 10% sodium hydroxide solution and steam distilled. The amine, 3-hydroxy-5-androstene-17-amine, separated as a solid which was removed by filtration and dried. The crude amine may be purified by recrystallization or by conversion to the benzal derivative as described in Example V.

Example XV

A solution of 3.0 g. of pregnenolone acetate oximino-p-toluenesulfonate in 60 cc. of ethanol in which 0.8 g. of sodium metal was previously dissolved was refluxed for two hours. The crude amine was separated by steam distillation of the alkaline reaction solution. The 3-hydroxy-5-androstene-17-amine was filtered, washed with water and dried. It gave a benzal derivative which melted at 241-243° C.

Example XVI

3.5 g. of pregnenolone acetate oxime was converted to the p-toluenesulfonate by treatment with 2.5 g. of p-toluenesulfonyl chloride in 15 cc. of ole pyridine. After standing at room temperature for three hours excess pyridine was removed in good vacuum with gentle warming and the residue dissolved in 50 cc. of methanol. The solution was refluxed for three hours. The methanol was removed and the residue dissolved in ether and washed with dilute sodium hydroxide solution. Concentration of the ethereal solution gave the crude 3-acetoxy-5-androstene-17-amine. It gave a benzal derivative which melted at 195-198° C. After recrystallization from benzene-methanol.

In the above procedure, n-propyl alcohol may be substituted for the methanol.

Example XVII

A solution of 1.3 g. of pregnenolone acetate oximino-p-toluenesulfonate in 15 cc. of n-propyl alcohol was heated on a steam bath for two hours. The amine was separated as described in Example XVI. Here the end result was the crude 3-hydroxy-5-androstene-17-amine

Example XVIII

3.0 g. of the p-toluenesulfonate of pregnenolone acetate oxime was suspended in 60 cc. of n-amyl alcohol containing sodium n-amylaldehyde (from 0.6 g. of sodium metal). The solution was refluxed for one and one-half hours and then steam distilled. The product, crude 3-hydroxy-5-androstene-17-amine, separated as a solid which was filtered, washed with water and dried. The amine purified either by recrystallization or through the benzal derivative melted at 163-166° C.

Example XIX

A solution of 3.74 g. of pregnenolone acetate oxime in 15 cc. of pyridine was treated with 3.74 g. of p-toluenesulfonyl chloride and then allowed to stand at room temperature for four hours. It was then poured over ice which had been acidified with 15 cc. of concd. sulfuric acid. The mixture was warmed on a steam bath for a short while before separation of the solid by filtration. The washed and dried solid was dissolved in 100 cc. of methanol containing 3 g. of potassium hydroxide. After refluxing for one hour the solution was steam distilled. 3-hydroxy-17-acetyl-amino-5-androstene separated as a crystalline

solid which was filtered, washed with water and dried. The recrystallized material melted at 268–270° C.

2.0 g. of the acetylamino compound was dissolved in 10 cc. of ethanolamine and heated on a steam bath. Since there was no apparent reaction, heating was continued for two hours in a metal bath at 170–180° C. The solution when cool was diluted with methanol and steam distilled. The crystalline solid was separated by filtration, washed with water and dried, 1.9 g. M. P. 262–266° C. It gave no depression in melting point when mixed with a sample of the original 3-hydroxy-17-acetylamino-5-androstene. Thus no reaction had taken place.

Example XX

A solution of 6.6 of i-pregnenolone methyl ether (6-methoxy-i-pregnene-20-one) in 100 cc. of methanol was treated with a solution of 4 g. of hydroxylamine hydrochloride and 6 g. of anhydrous sodium acetate in 20 cc. of water. The mixture was refluxed for one hour, diluted with water and extracted with ether. The ethereal solution was washed with water, diluted sodium carbonate solution, water and dried. After removal of the majority of the ether by distillation, the product was crystallized from ether-petr. ether (B. P. 35–60° C.). The crude i-pregnenolone methyl ether oxime, 5.6 g., was a white crystalline solid which melted at 172–185° C. The product after recrystallization from the same solvents, melted at 172–175° C. with some frothing, and clearing by 185° C.

Anal.—Calc'd. for $C_{22}H_{35}O_2N$: C, 76.47; H, 10.22. Found: C, 76.66; H, 10.28.

5.0 g. of the i-pregnenolone methyl ether oxime was dissolved in 20 cc. of pyridine. The solution was chilled in an ice bath and 5 g. of p-toluenesulfonyl chloride was added. After the chloride had dissolved in the cold solution, the mixture was placed in an ice-box for 15 hours. It was then poured into ice-water and extracted with benzene. The solution was washed well with cold water, dilute sulfuric acid, water, dilute sodium bicarbonate solution and water. The dried benzene solution was concentrated in partial vacuum to 20 cc. and product crystallized by the addition of petr. ether (B. P. 35–60° C.). The oximino-p-toluenesulfonate, 6.7 g., melted at 132–135° C., dec.

Anal.—Calc'd. for $C_{29}H_{41}O_4NS$: C, 69.72; H, 8.27. Found: C, 70.01; H, 8.45.

5.18 g. of i-pregnenolone methyl ether oximino-p-toluenesulfonate was dissolved in 30 cc. of ethanolamine and heated on the steam bath for two hours. The solution was then steam distilled and the residue diluted with water and extracted with ether. Upon removal of ether from the washed and dried ethereal solution, there remained 3.1 g. of crude 6-methoxy-i-androstene-17-amine, a yellow viscous oil. This amine formed a white crystalline salt with acetic acid melting at 170–173° C. (when placed in melting point bath at 155° C.).

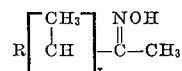
Comparison of Example XIX with the remaining examples indicates that the action of the acetyl acceptor is not simply to promote hydrolysis of the steroid acetyl amine, and that the amine is formed without going through the acetyl amine as an intermediate. The mechanism of the reaction, however, is not known beyond the fact that the end product is the acetyl derivative of the acceptor instead of the acetyl derivative of the steroid amine.

It is to be understood that the foregoing examples are illustrative and that various modifications may be made therein without departing from the invention. Thus other sulfonates than the p-toluene-sulfonate and benzene sulfonate may be used to esterify the oximino hydroxyl group. Where there are hydroxyl groups elsewhere in the molecule it is generally preferred to esterify them with less expensive esterifying agents than the sulfonic acids since if they are not previously protected they will be esterified along with the oximino hydroxyl group. However, the prior protection of these additional hydroxyl groups is not essential to the production of amines by the present invention, and in certain cases it may even be desirable to form polysulfonates which can undergo the amine rearrangement and simultaneous reaction involving the other sulfonate group.

From the foregoing it is seen that the rearrangement of the oximes of methyl-ketosteroids by carrying out the rearrangement on sulfonic acid esters thereof in the presence of the "acetyl acceptors" of the present inventions brings about advantageous results over the prior art method of degrading the side chain using the normal Beckmann rearrangement.

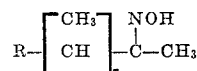
Having described the invention, what is claimed is:

1. The process for producing primary steroid amines which comprises effecting rearrangement of a sulfonic acid ester of an oxime of the formula



wherein R is a cyclopentanopolyhydrophenanthrene radical and x is a number chosen from the group consisting of zero and one by treating the same in the presence of a large amount of at least one compound selected from the group consisting of alcohols, primary amines, secondary amines, alcohol amines and diamines having a hydrogen atom attached to an amino nitrogen atom and mixtures thereof.

2. The process for producing primary steroid amines which comprises effecting rearrangement of a sulfonic acid ester of an oxime of the formula

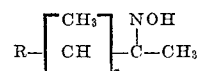


wherein R is a cyclopentanopolyhydrophenanthrene radical and x is a number chosen from the group consisting of zero and one, by treating the same in the presence of a large amount of an amine having a hydrogen atom attached to the amino nitrogen atom.

3. The process of claim 2 in which the amine is a primary amine.

4. The process of claim 2 in which the amine is a diamine.

5. The process for producing primary steroid amines which comprises effecting the rearrangement of a sulfonic acid ester of an oxime of the formula

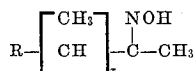


wherein R is a cyclopentanopolyhydrophenanthrene radical, and x is a number chosen from the group consisting of zero and one, by treating the same in the presence of a large amount of an alcohol having a hydrogen atom attached to the carbon atom carrying the hydroxyl group.

9

6. The process of claim 5 in which the alcohol is a primary alcohol.

7. The process for producing primary steroid amines which comprises effecting rearrangement of a sulfonic acid ester of an oxime of the formula



wherein R is a cyclopentanopolyhydrophenanthrene radical and x is a number chosen from the group consisting of zero and one, by treating the same in the presence of a large amount of an alkanolamine.

8. The process of claim 7 wherein the alkanolamine is a primary amine.

9. The process of claim 7 wherein the alkanolamine is a primary alcohol.

10. The process of claim 7 wherein the alkanolamine is ethanolamine.

11. The process of claim 1 wherein x is zero.

12. The process which comprises treating a solution of a sulfonic acid ester of pregnenolone acetate oxime in a compound selected from the class consisting of alcohols, primary amines, secondary amines, alcohol amines, and diamines having a hydrogen atom attached to an amino nitrogen and mixtures thereof.

13. The process which comprises heating a solution of a sulfonic acid ester of pregnenolone acetate oxime in an amine having a hydrogen atom attached to the amino nitrogen.

14. The process of claim 13 in which the amine is a primary amine.

15. The process which comprises heating a solution of a sulfonic acid ester of pregnenolone

10

acetate oxime in an alcohol having a hydrogen atom attached to the carbon atom carrying the hydroxyl group.

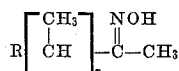
16. The process of claim 15 in which the alcohol is a primary alcohol.

17. The process which comprises heating an alkanolamine solution of a sulfonic acid ester of pregnenolone acetate oxime.

18. The process which comprises heating an ethanolamine solution of a sulfonic acid ester of pregnenolone acetate oxime.

19. The process of claim 1 in which x is one.

20. The process for producing primary steroid amines which comprises effecting rearrangement of a sulfonic acid ester of an oxime of the formula



wherein R is a cyclopentanopolyhydrophenanthrene radical and x is a number chosen from the group zero and one, by treating the same in the presence of a large amount of at least one compound selected from the class consisting of alcohols, primary amines, secondary amines, alcohol amines and diamines having a hydrogen atom attached to an amino nitrogen and mixtures thereof, and subjecting the resulting mixture to a steam distillation.

PERCY L. JULIAN.
JOHN W. COLE.
EDWIN W. MEYER.
ARTHUR MAGNANI.

No references cited.